No. 06-1249

Title:	Wyeth, Petitioner v. Diana Levine
Docketed:	March 14, 2007
Lower Ct:	Supreme Court of Vermont
Case Nos.:	(2004-384)
Decision Date:	October 27, 2006
Rehearing Denied:	December 11, 2006

Questions Presented

~~Date~~~	~~~~~~~~Proceedings and Orders~~~~~~~~~~~~~~~~~~~~~~~~~~
Mar 12 2007	Petition for a writ of certiorari filed. (Response due April 13, 2007)
Apr 9 2007	Order extending time to file response to petition to and including April 20, 2007.
Apr 20 2007	Brief amicus curiae of Pharmaceutical Research and Manufacturers of America filed.
Apr 20 2007	Brief amici curiae of Product Liability Advisory Council, Inc., et al. filed.
Apr 20 2007	Brief of respondent Diana Levine in opposition filed.
Apr 30 2007	Reply of petitioner Wyeth filed.
May 1 2007	DISTRIBUTED for Conference of May 17, 2007.
May 21 2007	The Solicitor General is invited to file a brief in this case expressing the views of the United States.
Dec 21 2007	Brief amicus curiae of United States filed.
Jan 2 2008	DISTRIBUTED for Conference of January 18, 2008.
Jan 2 2008	Supplemental brief of respondent Diana Levine filed. (Distributed)
Jan 2 2008	Supplemental brief of petitioner Wyeth filed. (Distributed)
Jan 16 2008	Letter received from the Solicitor General. (Distributed)
Jan 17 2008	Letter of January 17, 2008, from counsel for respondent received. (Distributed)
Jan 17 2008	Letter of January 17, 2008, from counsel for the petitioner received. (Distributed).
Jan 18 2008	Petition GRANTED. The brief of petitioner is to be filed on or before Monday, February 25, 2008. The brief of respondent is to be filed on or before Monday, March 24, 2008. A reply brief, if any, is to be filed in accordance with Rule 25.3 of the Rules of this Court.
Feb 15 2008	The time within which to file the joint appendix and petitioner's brief on the merits is extended to and including May 27, 2008.
Feb 15 2008	The time within which to file respondent's brief on the merits is extended to and including August 1, 2008.

May 27 2008 Joint appendix filed. Statement of costs received.

May 27 2008 Brief of petitioner Wyeth filed.

May 28 2008 Consent to the filing of amicus briefs, in support of either party or neither party, received from counsel for the petitioner.

May 30 2008 Brief amicus curiae of Product Liability Advisory Council, Inc. filed.

Jun 2 2008 Brief amicus curiae of United States filed.

Jun 3 2008 Brief amicus curiae of Generic Pharmaceutical Association filed.

Jun 3 2008 Brief amici curiae of Washington Legal Foundation, et al. filed.

Jun 3 2008 Brief amici curiae of John E. Calfee, et al. filed.

Jun 3 2008 Brief amici curiae of PhRMA and BIO filed.

Jun 3 2008 Brief amicus curiae of Chamber of Commerce of the United States of America filed.

Jun 3 2008 Brief amicus curiae of DRI - The Voice of the Defense Bar filed.

Jul 2 2008 Consent to the filing of amicus curiae briefs in support of either or neither party received from counsel for the respondent.

Jul 9 2008 The time within which to file respondent's brief on the merits is further extended to and including August 7, 2008.

Aug 7 2008 Brief of respondent Diana Levine filed. (Distributed).

Aug 8 2008 CIRCULATED.

Aug 12 2008 Motion of the Acting Solicitor General for leave to participate in oral argument as amicus curiae and for divided argument filed.

Aug 13 2008 Record received from the Supreme Court of Vermont. (2 boxes)

Aug 14 2008 Brief amici curiae of Former FDA Commissioners Dr. Donald Kennedy and Dr. David A. Kessler filed. (Distributed)

Aug 14 2008 Brief amici curiae of Kim Witczak, Sara Bostock, and Healthy Skepticism filed. (Distributed)

Aug 14 2008 Brief amicus curiae of DES Action filed. (Distributed)

Aug 14 2008 Brief amici curiae of Torts Professors Mark P. Gergen and Michael D. Green filed. (Distributed)

Aug 14 2008 Brief amici curiae of Anju Budhwani, M.D., et al. filed. (Distributed)

Aug 14 2008 Brief amici curiae of AARP, et al. filed. (Distributed)

Aug 14 2008 Brief amici curiae of Vermont, et al filed. (Distributed)

Aug 14 2008 Brief amici curiae of Members of Congress filed. (Distributed)

Aug 14 2008 Brief amici curiae of New England Journal of Medicine Editors and Authors filed. (Distributed)

Aug 14 2008 Brief amici curiae of Texas Medical Association, et al. filed. (Distributed)

Aug 14 2008 Brief amicus curiae of Center for State Enforcement of Antitrust and Consumer Protection Laws, Inc. filed. (Distributed).

Aug 14 2008 Brief amici curiae of David B. Ross, M.D. and Stefan P. Kruszewski, M.D. filed. (Distributed)

Aug 14 2008	Brief amici curiae of Daniel Paul Carpenter, et al. filed. (Distributed)
Aug 14 2008	Brief amicus curiae of American Association for Justice filed. (Distributed)
Aug 14 2008	Brief amicus curiae of Constitutional and Administrative Law Scholars filed. (Distributed)
Aug 14 2008	Brief amicus curiae of California Medical Association filed. (Distributed)
Aug 14 2008	Brief amicus curiae of National Coalition Against Censorship filed. (Distributed)
Aug 14 2008	Brief amicus curiae of National Conference of State Legislatures filed. (Distributed)
Aug 14 2008	Brief amicus curiae of Constitutional Accountability Center filed. (Distributed)
Aug 14 2008	Brief amicus curiae of Consumers Union of the United States filed. (Distributed)
Aug 14 2008	Brief amicus curiae of Senior Citizens League filed. (Distributed)
Aug 14 2008	Brief amicus curiae of Citizens Commission on Human Rights filed. (Distributed)
Aug 18 2008	SET FOR ARGUMENT ON Monday, November 3, 2008
Aug 26 2008	Application (08A169) to extend the time to file a reply brief on the merits from September 8, 2008 to September 15, 2008, submitted to Justice Ginsburg.
Aug 26 2008	Application (08A169) granted by Justice Ginsburg extending the time to file a reply brief on the merits until September 15, 2008.
Aug 27 2008	Additional record received from the Supreme Court of Vermont. (1 box)
Aug 27 2008	Letter, dated August 27, 2008, received from the Acting Solicitor General.
Sep 15 2008	Reply of petitioner Wyeth filed. (Distributed)
Oct 6 2008	Motion of the Acting Solicitor General for leave to participate in oral argument as amicus curiae and for divided argument GRANTED.
Oct 30 2008	Letter from counsel for respondent proposing to lodge copies of a newly issued congressional staff report of the Committee on Oversight and Government Reform.
Oct 31 2008	Response from counsel for petitioner to respondent's proposed lodging. Distributed.
Oct 31 2008	The Clerk has approved respondent's proposed lodging. 20 copies of congressional staff report of the Committee on Oversight and Government Reform received and distributed.
Nov 3 2008	Argued. For petitioner: Seth P. Waxman, Washington, D.C.; and Edwin S. Kneedler, Deputy Solicitor General, Department of Justice, Washington, D.C. (for Untied States, as amicus curiae.) For respondent: David C. Frederick, Washington, D.C.

Supreme Court, U.S.
FILED

No. 06- 061249

MAR 12 2007
OFFICE OF THE CLERK

IN THE

Supreme Court of the United States

WYETH,

Petitioner,

v.

DIANA LEVINE,

Respondent.

ON PETITION FOR A WRIT OF CERTIORARI
TO THE SUPREME COURT OF THE STATE OF VERMONT

PETITION FOR A WRIT OF CERTIORARI

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QUESTION PRESENTED

Whether the prescription drug labeling judgments imposed on manufacturers by the Food and Drug Administration ("FDA") pursuant to FDA's comprehensive safety and efficacy authority under the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 301 *et seq.*, preempt state law product liability claims premised on the theory that different labeling judgments were necessary to make drugs reasonably safe for use.

LIST OF PARTIES

Pursuant to Rule 14.1(b), the following list identifies all of the parties to the appellate proceeding in the Supreme Court of Vermont, whose judgment is sought to be reviewed:

A. Petitioner

Wyeth

B. Respondent

Diana Levine

CORPORATE DISCLOSURE STATEMENT

Petitioner Wyeth has no parent corporation, and no publicly held company owns 10% or more of its stock.

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The decision of the Supreme Court of Vermont is reported at -- A.2d -- (Vt. 2006) and reprinted in the Appendix ("App.") at 1a-48a. The trial court's decision denying Petitioner's Motion for Judgment as a Matter of Law is reprinted at App. 49a-74a.

JURISDICTION

The Supreme Court of Vermont rendered its decision on October 27, 2006, App. 1a, and denied a timely motion for reargument on December 11, 2006, App. 75a. This Court has jurisdiction under 28 U.S.C. § 1257(a).

PERTINENT CONSTITUTIONAL, STATUTORY, AND REGULATORY PROVISIONS

The pertinent constitutional, statutory, and regulatory provisions are set forth in the Appendix, App. 77a-138a.

INTRODUCTION

Granting this petition would enable the Court to resolve the pervasive and recurring conflict between state claims of power to regulate prescription drug labeling and the integrity of the congressionally mandated federal prescription drug labeling regime that lies at the heart of the Food and Drug Administration's ("FDA's") regulatory authority. This conflict is currently at issue in tens of thousands of cases in our nation's courts, in which plaintiffs claim that manufacturers should have modified FDA-approved prescription drug labeling. The lower courts have resolved this conflict inconsistently and have given varying weight to FDA's formal statements on the extent to which such claims obstruct its regulatory objectives. A ruling by this Court on the preemption issues presented would provide invaluable guidance to the hundreds of federal and state judges now grappling with these claims.

In this case, Wyeth's federally approved labeling of its anti-nausea drug Phenergan reflected FDA's expert judgment that the option to administer the drug intravenously by direct, or

"push," ("IV push") injection[1] – which provides faster and more potent relief than other methods of administration – should be preserved. Respondent was injured when Phenergan was administered to her by IV push injection and somehow came in contact with arterial blood, causing gangrene and the loss of her forearm. App. 2a. The approved labeling repeatedly and prominently warned of the hazard of arterial exposure, expressly stating that, should a health care provider determine that IV push injection was warranted, he or she must use "extreme care" not to introduce the medicine into the patient's arteries to avoid serious injuries, including "gangrene requiring amputation," which was "likely under such circumstances." App. 167a. Respondent claimed that Phenergan's labeling should have gone further and foreclosed IV push injection altogether in light of the risk of injury. Wyeth countered that Respondent's claim was preempted under federal law.

Over the strong dissent of Chief Justice Reiber, a Vermont Supreme Court majority held that Respondent's claim was not preempted by FDA's decisions to preserve the IV push injection option because Wyeth was not absolutely barred from implementing labeling changes without FDA's prior approval. The majority reasoned that Wyeth could have – and, as the jury found, should have – foreclosed IV push injection. It also declined to consider Wyeth's contention that the duty to bar IV push injection imposed by Vermont law would obstruct the purposes and objectives of FDA's supervision of Phenergan's labeling, concluding that this line of traditional preemption analysis was precluded by a savings clause in the Federal Food, Drug and Cosmetic Act ("FDCA"). App. 21a-24a. In reaching its decision, the majority rejected FDA's unequivocal position that claims precisely like Respondent's disrupted the agency's ability to ensure that prescribers receive the best information on how to balance the risks and benefits of methods of drug administration. App. 24a-28a.

[1] IV push injections are administered by applying pressure to inject a drug into a patient's veins and differ from "IV drip" administration, where a drug is slowly "dripped" into a patient's veins from a hanging IV bag.

The Vermont Supreme Court's decision is in error. If allowed to stand, it would empower courts to review and override FDA's careful and comprehensive balancing of safety and effectiveness concerns in prescription drug labeling and to undermine the integrity of FDA's statutorily mandated labeling regime – as the expert agency has recognized. This Court should grant review to restore the proper balance between federal and state authority in this critical area affecting the nation's public health.

STATEMENT OF THE CASE

A. Factual Background

1. FDA Regulatory Regime

Congress has established FDA as the sole federal agency commissioned both to "protect the public health" by ensuring that drugs are safe and effective and to "promote the public health" by ensuring prompt public access to drugs it has found to be safe and effective. 21 U.S.C. § 393(b). FDA's power to ensure the safety of drugs and their labeling dates back to the 1938 Federal Food, Drug and Cosmetic Act ("FDCA"), in which Congress first charged FDA to: (a) serve as the sole gatekeeper for deciding whether a drug is safe for its labeled uses and includes "adequate directions for [such] use"; and (b) seize drugs it finds are inadequately labeled or dangerous when used as intended. *See* Pub. L. No. 75-717, §§ 201(p), 301(a), 502(f), 505(d)(1), 52 Stat. 1040, 1041-42, 1051-52 (1938) (codified as amended at 21 U.S.C. §§ 321(p), 331(a), 352(f), 355(d)). Marketing a prescription drug with a label that is not FDA-approved is a federal crime. *See* 21 U.S.C. §§ 332(a), 333(a), 334.

Since 1962, Congress also has entrusted FDA with ensuring that safe drugs are effective for their labeled uses. *See* Drug Amendments of 1962, Pub. L. No. 87-781, § 102(b), 76 Stat. 780, 781 (1962) (codified as amended at 21 U.S.C. § 355(b)). This significant expansion of FDA's regulatory oversight authority recognized that the use of any drug entails some risk and that marketing approval should rest on FDA's scientific determination that a drug's overall health care benefit outweighs its risks. *See* S. Rep. No. 87-1744, at 15 (1962), *as reprinted in*

1962 U.S.C.C.A.N. 2884, 2891-92 (observing that, for very risky drugs, "the determination of safety is, in the light of the purposes of the new drug provisions, considered by [FDA] to be inseparable from consideration of the drug's effectiveness"); Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products, 71 Fed. Reg. 3922, 3934 (Jan. 24, 2006), App. 128a ("Under the Act and FDA regulations, the agency makes approval decisions based . . . on a comprehensive scientific evaluation of the product's risks and benefits under the conditions of use prescribed, recommended, or suggested in the labeling." (citation omitted)). Balancing risks against benefits for particular prescription drugs, dosages, and methods of administration thus has been the central task of FDA for nearly a half-century.

As FDA has repeatedly made clear, the agency conducts this risk-benefit assessment from a forward-looking perspective, with the overall public health in mind, rather than through the prism of individual cases. As a former Commissioner has testified:

> Every time the scientists on our staff allow a new drug to come to market, they have to take the sum total of scientific knowledge that they can muster about the drug, and reach a conclusion as to whether or not the good that the drug will do, the lives it will save or the suffering that it will prevent, outweighs the known side-effects.

See Hearing on H.R. 6245 Before the Subcomm. On Antitrust of the H. Comm. On the Judiciary, 87th Cong. 135 (1962) (statement of George P. Larrick, Commissioner, FDA); *see also* FDA, *Draft Guidance for Industry: Development and Use of Risk Management Action Plans* 4 (Mar. 2005), *available at http://www.fda.gov/cder /guidance/6358fnl.pdf* (describing FDA's risk-benefit assessment as measuring whether, under labeled conditions of use, "the clinical significance and probability of [a drug's] beneficial effects outweigh the likelihood and medical importance of its harmful or undesirable effects").

To obtain FDA approval of a new prescription drug, the manufacturer must submit a New Drug Application ("NDA"). *See* 21 U.S.C. § 355(b). As part of the NDA, the manufacturer

must submit comprehensive information concerning the new drug, "full reports of investigations" concerning safety and effectiveness, and "specimens of the labeling proposed to be used for such drug." *Id.* § 355(b)(1); 21 C.F.R. § 314.50. The information submitted must establish that the new drug is safe and effective "for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof" before FDA will approve it for distribution and marketing. 21 U.S.C. § 355(d)(1).

The review and approval of a drug's labeling therefore is a critical means through which FDA carries out its risk-benefit assessment. *See* New Drug and Antibiotic Regulations, 50 Fed. Reg. 7452, 7470 (Feb. 22, 1985) ("Drug labeling serves as the standard under which FDA determines whether a product is safe and effective."); *see also* FDA, *Guidance: Drug Safety Information – FDA's Communication to the Public* 7 (Mar. 2007), *available at* http://www.fda.gov/cder/guidance/7477fnl.pdf ("FDA-approved drug product labeling is the primary source of information about a drug's safety and effectiveness . . . ."). For this reason, FDA has issued a series of regulations that comprehensively dictate the form and substance of all prescription drug labels. Those drug labels must include, among a host of other requirements, "a summary of the essential scientific information needed for safe and effective use of the drug," 21 C.F.R. § 201.56(1), including a description of "clinically significant adverse reactions," "other potential safety hazards," "limitations in use imposed by them, . . . and steps that should be taken if they occur," *id.* § 201.57(c)(6)(i). Accordingly, FDA's approval of an NDA is inseparable from the agency's approval of the precise language contained on the new drug's label. *See id.* § 314.50(e)(2)(ii), (*l*)(1)(i).

FDA's regulatory authority over prescription drug labeling continues after a drug is initially approved for marketing and distribution. Manufacturers have an ongoing obligation to submit reports "of data relating to clinical experience" –

including adverse drug events. 21 U.S.C. § 355(k)(1); *see also* 21 C.F.R. § 314.80. FDA has the authority to withdraw a drug from the market if it concludes the drug is unsafe or ineffective for its labeled uses. *See* 21 U.S.C. § 355(e). Although manufacturers may initiate labeling changes, they must submit to FDA full descriptions of all proposed changes and ordinarily await FDA approval before implementing a proposed change. *See id.* § 355(b)(1)(F); 21 C.F.R. § 314.70. FDA has, however, adopted a regulation – known as the "change being effected," or "CBE," provision – that extraordinarily allows manufacturers to initiate interim post-approval labeling changes pending FDA approval. The CBE provision is designed to operate only when scientifically significant, newly discovered information demands changes to: (a) add or strengthen a contraindication, warning, precaution, or adverse reaction; or (b) add or strengthen an instruction about dosage and administration intended to increase safe use of a drug. *Id.* § 314.70(c)(6)(iii)(A), (C). CBE changes are interim; "the determination whether labeling revisions are necessary is, in the end, squarely and solely FDA's under the act." 71 Fed. Reg. at 3934, App. 132a.

2. FDA's Regulation of Phenergan

Wyeth sold injectable Phenergan for treatment of nausea. FDA found injectable Phenergan safe for labeled conditions of use and approved it for sale with no limitation on any method of IV injection in 1955. In 1967, Wyeth first received a report of gangrene and subsequent amputation resulting from arterial blood exposure to Phenergan, which it reported to FDA. App. 139a. At that time, Phenergan's labeling already warned against such arterial blood exposure through perivascular extravasation or intra-arterial injection.[2] App. 139a-140a.

Between 1967 and 1981, FDA worked closely with Wyeth

[2] Perivascular extravasation occurs when a drug administered intravenously leaks out of the vein into the surrounding tissue, where it may come into contact with arterial blood. App. 4a, 42a. Perivascular extravasation occurs through no fault of the physician or the drug manufacturer. App. 42a.

through a series of communications and at least one in-person meeting to refine Phenergan's warnings with respect to IV push administration. As of at least 1974, Phenergan's label made clear that intramuscular ("IM") injection was the "preferred parenteral route of administration" and advised that IV administration was "well-tolerated" but "not without some hazard" because gangrene could result from exposure of Phenergan to arterial blood. App. 53a.

As of 1981, the Phenergan label included the following language: "When administering any irritant drug intravenously, it is usually *preferable* to inject it through the tubing of an intravenous infusion set that is known to be functioning satisfactorily" — *i.e.*, through IV drip administration. App. 54a (emphasis added). While FDA noted its preference for the IV drip method, it never suggested that the IV push method of injection should be contraindicated or foreclosed.

In 1987, after Wyeth complied with a general FDA mandate to reformat Phenergan's labeling and submit it by a supplemental New Drug Application ("sNDA") for approval, FDA recommended revisions concerning the "recognition and management of unintended intra-arterial injection." App. 150a-157a. These changes included an enhanced instruction concerning IV drip administration: "Injection through a properly running intravenous infusion [set] may enhance the possibility of detecting arterial placement. In addition, this results in delivery of a lower concentration of any arteriolar irritant." App. 152a. Again, however, FDA never suggested that the IV push method should be contraindicated or foreclosed.

On May 3, 1988, Wyeth submitted new draft labeling for FDA approval that essentially incorporated FDA's recommended changes relating to IV drip administration: "Injection into an intravenous infusion set that is known to be running properly should decrease the possibility of inadvertently injecting

promethazine intra-arterially. In addition, this results in delivery of a lower concentration of any arteriolar irritant." App. 54a.

In 1997 – explaining that it had taken extra time to review Phenergan's proposed labeling changes to ensure that it had "dotted every 'i' and crossed every 't'" – FDA specifically ordered Wyeth to "[r]etain [the] verbiage in [the] current label" concerning inadvertent intra-arterial injection and to make other labeling changes. App. 158a-159a, 162a. Wyeth submitted a revised draft package insert on May 8, 1998 in compliance with FDA's orders. FDA then approved that labeling and expressly commanded Wyeth that "[t]he final printed labeling (FPL) for the package insert *must be identical to the draft package insert submitted May 8, 1998*." App. 165a (emphasis added).

FDA's consistent decision not to foreclose IV push administration of Phenergan reflected a classic balancing of risks and benefits. The beneficial effects of IV injection generally begin within five minutes; IV drips (when equipment is available) are slower to administer, and IM injection can require twenty minutes or more to take effect. App. 165a. This is no small difference: extreme nausea can cause a patient to lose fluids quickly, which leads to dehydration, a serious medical condition. A doctor, confronted with a patient in dire need of relief from nausea, could reasonably decide that the benefits of IV push administration would warrant taking its increased risk.[3]

3. The Operative Phenergan Label when Respondent Was Treated

In 2000, as a result of the foregoing FDA oversight over a 45-year period and a series of revisions, Phenergan's two-page label included repeated, prominent notice of the risk of gangrene arising from inadvertent arterial exposure in no fewer than four

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[3] Moreover, under certain circumstances, IM injection is unreliable or ineffective, such as in the treatment of overweight patients and patients with poor blood flow to the various muscle groups due to dehydration or cardiac disease. In such a situation, a doctor could determine that IV push injection is the only way to provide the patient with the needed relief.

separate sections – *i.e.*, "Contraindications," "Warnings," "Adverse Reactions," and "Dosage and Administration." Two such sections provided the following notice in upper-case type:

> **INADVERTENT INTRA-ARTERIAL INJECTION CAN RESULT IN GANGRENE OF THE AFFECTED EXTREMITY.**

App. 4a, 167a. The label further warned that:

> Due to the close proximity of arteries and veins in the areas most commonly used for intravenous injection, extreme care should be exercised to avoid perivascular extravasation or inadvertent intra-arterial injection. Reports compatible with inadvertent intra-arterial injection of Phenergan Injection, usually in conjunction with other drugs intended for intravenous use, suggest that pain, severe chemical irritation, severe spasm of distal vessels, and resultant gangrene requiring amputation are likely under such circumstances.

App. 4a, 167a. The label also included lengthy instructions concerning the means of minimizing this risk in both the "Dosage and Administration" and "Warnings" sections. App. 167a.

4. The Administration of Phenergan to Respondent

On April 7, 2000, Respondent sought treatment from Northeast Washington County Community Health, Inc. (the "Health Center") for a severe migraine headache and associated nausea and dehydration. App. 2a. Respondent was initially treated with Phenergan via IM injection, the preferred method of administration. App. 2a.

Respondent returned to the Health Center later that day because she had not obtained effective relief. App. 2a. A second dose of Phenergan was then administered directly into Respondent's vein via IV push injection. App. 2a. Phenergan's FDA-approved label specifically instructed practitioners to proceed with extreme caution in any administration; the administering physician assistant was aware of these instructions and of the risk of arterial exposure through misinjection.

Respondent thereafter developed the symptoms of arterial exposure and had to have her forearm amputated. App. 2a. Before the commencement of this case, Respondent sued the health care providers for malpractice and settled for $700,000.

B. Proceedings Below

1. The Trial Court Proceedings

Respondent brought state-law-based liability claims against Wyeth on the theory that Wyeth should have revised Phenergan's FDA-approved label to bar IV push administration. App. 38a, 41a. The jury returned a verdict in favor of Respondent, who was ultimately awarded $ 6,774,000. App. 3a.

Wyeth sought judgment as a matter of law on the ground that federal law preempted Respondent's claims. The trial court denied Wyeth's motion, issuing an opinion independently addressing preemption as a matter of law. App. 4a, 74a. In its view, FDA's CBE regulation, 21 C.F.R. § 314.70, "permit[s] strengthened warnings without approval on an interim basis," App. 64a, such that Wyeth could be required to conform its labeling to common law tort duties. The court acknowledged the inevitable differences between FDA's comprehensive balancing of public safety and efficacy interests and the tort process, which views "the matter in hindsight through the lens of a single catastrophic case," App. 62a, but still found that the jury's state-law-based judgment presented no obstacle to FDA's regulatory objectives, App. 63a.

2. The Appeal to the Vermont Supreme Court

Wyeth timely appealed to the Vermont Supreme Court. Wyeth contended that the trial court erred, *inter alia*, by failing to hold that Respondent's common law claims were preempted because: (1) Wyeth would have been unable to comply with both Vermont's common law duty to foreclose IV push injection and FDA's directive, as evidenced by the drug's approved label, to retain it; and (2) the claims would obstruct the full accomplishment of FDA's risk-benefit objective to optimize use of Phenergan by imposition of a duty to foreclose IV push injection. App. 5a-6a. The Vermont Supreme Court rejected both

arguments and affirmed the trial court's decision. App. 19a, 28a.

The court first rejected Wyeth's claim that it would be impossible for Wyeth to comply with both a Vermont common law duty to foreclose IV push injection and a federal duty to use an FDA-approved label that allowed the drug to be administered in this fashion. Like the trial court, the Supreme Court relied on the CBE regulation, 21 C.F.R. § 314.70(c). In the court's view, "FDA approval of a particular label does not preempt a jury finding that the label provided insufficient warning, as defendant was free under § 314.70(c) to strengthen the warning without prior FDA approval." App. 17a. The court also declined to accord any significance to FDA's directive to Wyeth to "[r]etain verbiage in current label." App. 17a.

The court next refused to consider Wyeth's claim that Vermont's decision to impose a state tort law duty on Wyeth created an obstacle to the objectives of the FDA regulatory regime. The court held that all such "obstacle" preemption claims were foreclosed by language in the 1962 amendments to the FDCA that premised preemption on a "direct and positive conflict between such amendments and [a] provision of State law." App. 21a (quoting Drug Amendments of 1962, § 202, 76 Stat. at 793, App. 112a). The court reasoned that section 202 restated the standard for "impossibility" preemption and thus "remove[d] from . . . consideration the question of whether common-law tort claims present an obstacle to the purposes and objectives of Congress." App. 21a.

Last, the court refused to give any weight to FDA's formal preemption analysis. Specifically, in a regulatory preamble to recent amendments to its labeling rule, FDA rejected the positions adopted by many federal courts and the Vermont Supreme Court that (1) section 314.70 broadly permits manufacturers to make unilateral labeling changes and (2) "[s]tate law serves as an appropriate source of supplementary safety regulation for drugs by encouraging or requiring manufacturers to disseminate risk information beyond that required by FDA under the act." App. 24a (quoting 71 Fed.

Reg. at 3934, App. 126a). To the court, FDA's analysis was "neither an authoritative interpretation of an ambiguous statutory provision entitled to deference, nor a persuasive policy statement entitled to respect." App. 28a (internal citation omitted).

Chief Justice Reiber dissented. The Chief Justice first concluded that an "actual conflict" existed between the jury verdict and federal law because "the FDA clearly addressed the risks attending IV administration of the drug[,] . . . approved IV administration generally, and specifically warned of the dangers of direct IV administration, including inadvertent arterial injection possibly resulting in amputation." App. 38a. "These assessments are, in fact, the very essence of the FDA's approval and are in furtherance of the federal objective of advancing public health by balancing the risks and benefits of new drugs and facilitating their optimal use." App. 38a.

The Chief Justice also found that Wyeth was not "'free' to change drug labels under [section] 314.70" because the purpose of this regulatory provision "is to allow manufacturers to address newly discovered risks." App. 39a-40a. Here, not only was there a complete absence of new evidence concerning IV push administration of Phenergan, but "FDA had already evaluated the risk of inadvertent arterial injection . . . and had mandated warning language for the label to reflect that risk assessment" in its 1997 directive to Wyeth. App. 40a. Wyeth thus "could not both list all forms of IV administration as an approved use, as required by the FDA, and exclude all or some forms of IV administration as unsafe, as required by the jury's verdict in this case." App. 43a.

The Chief Justice next rejected the majority's view that the section 202 "direct and positive conflict" language forbade the court from assessing whether state tort law obstructed the federal purposes and objectives served by FDA's regulatory regime. App. 44a-45a. On the merits of Wyeth's argument, the Chief Justice concluded that "obstacle preemption" applied in this case under the reasoning of *Geier v. American Honda Motor Co.*, 529 U.S. 861 (2000). App. 45a. The Chief Justice

analogized the federal safety standard at issue in *Geier* – which "allow[ed] a choice of passive restraint systems while not mandating any particular system" and "was a deliberate decision that reflected a balance of diverse policy concerns" – with FDA's risk-benefit balancing judgment, which "considers various policy factors that are sometimes in tension with one another" to "maximize the availability of beneficial treatments." App. 48a. According to the Chief Justice, FDA's conclusion that "Phenergan is safe and effective when delivered through IV administration" preempts any tort duty that would require Wyeth to bar that particular use. App. 48a.

REASONS FOR GRANTING THE PETITION

The Vermont Supreme Court held that a manufacturer may be liable under state law for failing to bar a particular method of administration of a prescription drug. The federal agency expert in evaluating the safety and efficacy of drugs had concluded that this highly potent method of administration should remain available and directed the manufacturer to retain a label that, while urging prescribers to use extreme care in administering the drug, nonetheless retained it as a medical option. This case thus presents a direct conflict between the considered labeling decision of a federal agency exercising its *ex ante* responsibility to make comprehensive public health judgments and an *ex post* case-specific determination of one state jury that the federally approved labeling was inadequate.

Unfortunately, this conflict is far from uncommon. There are tens of thousands of individual claims, and potentially millions of class action claims, currently pending in the lower federal and state courts, in which plaintiffs contend that a manufacturer's use of FDA-approved labeling for its prescription drug is inadequate to satisfy state-law duties to warn.[4] Divided lines of authority already have emerged and are

[4] *See, e.g., In re Bextra & Celebrex Marketing, Sales Practices & Prods. Liab. Lit.*, No. 05-cv-01699-CRB (N.D. Cal.) (litigation consists of over 1,800 lawsuits); *In re Prempro Prods. Liab. Litig.*, No. 4:03CV01507 (E.D. Ark.); *In re Vioxx Marketing, Sales Practices &* (Cont'd)

highly unlikely to be reconciled by further lower court decisions. By deciding key preemption issues here on a record that squarely and cleanly presents them,[5] this Court can forestall erroneous decisions in numerous cases and the huge expenditure of resources required to correct those errors and reprocess the underlying cases.

The Vermont Supreme Court made basic and fundamental doctrinal errors in its preemption analysis. Wyeth has consistently argued that a jury verdict premised on the alleged inadequacy under state law of an FDA-approved prescription drug label is preempted when it "actually conflicts" with the federal drug labeling regime. State law "actually conflicts" with federal law when "compliance with both federal and state regulations is a physical impossibility," *Florida Lime & Avocado Growers, Inc. v. Paul*, 373 U.S. 132, 142-43 (1963), or when state law "stands as an obstacle to the accomplishment and execution of the full purposes and objectives of Congress," *Hines v. Davidowitz*, 312 U.S. 52, 67 (1941). These bedrock principles apply with equal force to federal regulations, *see Fidelity Federal Savings & Loan Ass'n v. de la Cuesta*, 458 U.S. 141, 153 (1982), and do not differentiate between common law rules arising from state jury verdicts and positive legislative enactments, *see Cipollone v. Liggett Group, Inc.*, 505 U.S. 504, 522 (1992). Prescription drug labeling cases implicate both species of conflict preemption.

Determining whether state tort claims "actually conflict"

(Cont'd)

Prods. Liab. Litig., No. 05-MDL-1657 (E.D. La.) (approximately 27,400 lawsuits, including over 46,100 plaintiff groups, and approximately 264 putative class actions as of December 2006). Individual suits like that presented here are almost too numerous to count.

[5] This case presents an ideal vehicle for resolving these legal issues because the facts underlying the preemption question are not in dispute. There is no allegation that Wyeth had failed to react to safety information not considered by FDA or that Wyeth breached any other state law duty that might make the Vermont Supreme Court's mistaken preemption analysis insufficient to reverse the judgment.

with FDA prescription drug labeling rules requires resolution of three key legal questions. *First*, does FDA's labeling regime developed under congressional mandate provide only a minimum safety standard open to unlimited state supplementation or a fully calibrated risk-benefit balance of national applicability that state law should not disrupt? *Second*, are principles of "obstacle" conflict preemption trumped in prescription drug cases either by a presumption against preemption or by a statutory requirement that preemption arise from a "direct and positive" conflict? *Third*, should weight be given in the preemption analysis to FDA's recent formal assessment of the adverse impact of tort actions on the integrity of its labeling regime?

The Vermont Supreme Court answered all of these questions incorrectly. *First*, it concluded – contrary to the agency's view of its own regulations – that FDA's labeling requirements merely provided a "floor" and that a manufacturer was free unilaterally to change its labeling without prior FDA approval. *Second*, the court erroneously declined even to consider whether the state tort law duty would "stand as an obstacle" to the effectiveness of federal drug regulation, mistakenly reading a provision in the FDCA as precluding this entire line of traditional preemption analysis. *Finally*, the court dismissed FDA's carefully considered judgment that tort suits like the instant one disrupt the agency's ability to ensure that the optimal information about the risks and benefits of using prescription drugs is provided to prescribers. Each of these conclusions was erroneous, and each independently warrants reversal.

I. The Court Should Grant Review To Correct Vermont's Rejection of Impossibility Conflict Preemption Stemming from its Mischaracterization of FDA's Comprehensive Regulatory Regime.

The Vermont Supreme Court's opinions in this case exemplify an ongoing dispute in the lower courts as to whether FDA's labeling approvals establish only a minimum requirement ("floor") for safety-related disclosures or, alternatively, a

calibrated approach ("floor and ceiling") that neither underwarns nor overdeters effective use. This base disagreement is very often outcome determinative and has been characterized by FDA as a threat to the integrity of its comprehensive regulatory regime. *See* 71 Fed. Reg. at 3934, App. 130a ("FDA has learned of several instances in which product liability lawsuits have directly threatened the agency's ability to regulate manufacturer dissemination of risk information for prescription drugs in accordance with the act.").

A majority of the Vermont Supreme Court adopted the former view in this case, following a line of cases holding that "FDA's drug labeling decisions impose only 'minimum' standards that are open to supplementation by state law through a jury's verdict enforcing a manufacturer's common law duty to warn." *Caraker v. Sandoz Pharm. Corp*, 172 F. Supp. 2d 1018, 1033 (S.D. Ill. 2001); *Mazur v. Merck & Co.*, 742 F. Supp. 239, 247 (E.D. Pa. 1990) ("Manufacturers must meet state safety requirements, whether codified or embodied in the common law, in addition to satisfying initial FDA requirements."); *Cartwright v. Pfizer, Inc.*, 369 F. Supp. 2d 876, 883 (E.D. Tex. 2005) ("FDA only sets forth minimum standards for labeling and safety of drugs."); *McNellis v. Pfizer, Inc.*, No. Civ. 05-1286, 2005 WL 3752269, at *7 (D.N.J. Dec. 29, 2005) ("FDA's regulations do not conflict with New Jersey's failure to warn law because those federal regulations merely set minimum standards with which manufacturers must comply."), *stay granted and motion to certify appeal granted*, No. Civ. 05-1286 (JBS), 2006 WL 2819046 (D.N.J. Sept. 29, 2006). Under this approach, state labeling requirements – whether imposed through positive legislative enactments or judicial decree – can almost never be incompatible with FDA's labeling regime. App. 15a ("When further warnings become necessary, the manufacturer is at least partially responsible for taking additional action, and if it fails to do so, it cannot rely on the FDA's continued approval of its labels as a shield against state tort liability.").

Chief Justice Reiber's dissent looked to different authority holding that "inadequate warning claim[s] would . . . conflict

with the federal requirements imposed during the regulation of the prescription drug by, "in effect, allowing a state regulation to impose labeling requirements contrary to those required by federal law." *Needleman v. Pfizer, Inc.*, No. 3:03-CV-3073-N, 2004 WL 1773697, at *2 (N.D. Tex. Aug. 6, 2004); *In re Bextra & Celebrex Marketing Sales Practices & Prod. Liab. Litig.*, No. 05-1699, 2006 WL 2374742, at *10 (N.D. Cal. Aug. 16, 2006) ("Plaintiffs' state law failure-to-warn-claims conflict with the FDA's determination of the proper warning and pose an obstacle to the full accomplishment of the objectives of the FDCA."); *Ehlis v. Shire Richwood, Inc.*, 233 F. Supp. 2d 1189, 1198 (D.N.D. 2002) (finding that prescription drug warning claim was preempted where "FDA dictates the contents of the label" and where "defendants were prohibited from changing it without prior approval from the FDA, except in limited circumstances for a limited period of time"), *aff'd*, 367 F.3d 1013 (8th Cir. 2004).

As Chief Justice Reiber explained, it would have been literally impossible for Wyeth to have complied with both the duty newly imposed under Vermont common law and FDA's command that Phenergan be marketed under labeling identical to that submitted by Wyeth on May 8, 1998. Respondent's cause of action originated from – and this case ultimately turned on – the premise that Phenergan's labeling should have foreclosed IV push administration of Phenergan. App. 37a ("[W]hat plaintiff sought was an elimination of a use of Phenergan that had been approved by the FDA.") (Reiber, C.J., dissenting). Thus, Wyeth could have complied with the legal duty it allegedly breached under Vermont law only if it had modified its FDA-approved label without prior FDA authorization before April 7, 2000, when Respondent was injected. Unless federal law permitted such modification, well-established conflict preemption principles would preclude holding Wyeth liable for failing to follow a state mandate that would have forced it to violate federal law. *See Freightliner Corp. v. Myrick*, 514 U.S. 280, 287 (1995).

No FDCA provision authorizes manufacturers to modify FDA-approved labeling without prior FDA consent. Indeed, as the Vermont Supreme Court acknowledged, the FDCA conditions the right to ship prescription drugs in interstate commerce on the use of FDA-approved labeling. As FDA routinely advises manufacturers receiving New Drug approvals, "[m]arketing the product with [labeling] that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug." *Letter from Edward Cox, Acting Director, Center for Drug Evaluation and Research, to David Hallinan, VP Regulatory Affairs, Idenix Pharms., Inc.* (Oct. 25, 2006), *available at* http://www.fda.gov/cder/foi/appletter/2006/022011 5000ltr.pdf (approving NDA 22-011 (Tyzeka)); *see also* App. 165a (commanding that Phenergan's "final printed labeling . . . must be identical to the [FDA-approved] draft package insert"). Marketing a misbranded or unapproved prescription drug would subject the manufacturer to substantial criminal and civil penalties. 21 U.S.C. §§ 332(a), 333(a), 334.

To meet the need to disseminate newly discovered safety information without delay, FDA adopted its "change being effected," or "CBE," regulation, 21 C.F.R. § 314.70(c)(6)(iii), in 1982. Rather than properly interpreting that regulation as a limited exception to FDCA's pre-approval labeling regime, however, courts adopting the "minimum" standards approach have seized on it to open the door to far-reaching state safety regulation. The CBE regulation describes certain categories of interim labeling changes that manufacturers may make without prior FDA approval, including "[t]o add or strengthen an instruction about dosage or administration that is intended to increase the safe use of the drug product." *Id.* § 314.70(c)(6)(iii)(C). Under the Vermont court's construction, this regulation allows "unilateral changes to drug labels whenever the manufacturer believes it will make the product safer, and places no limit on the duration of pre-approval warnings unless the FDA disapproves of the change." App. 13a (citation omitted); *see also Caraker*, 172 F. Supp. 2d at 1034 ("Even after approval, additional or more forceful warnings may,

in the drug manufacturer's judgment, be added to labeling *without prior FDA approval* and on the drug manufacturers' own initiative."). Thus, "[w]hile specific federal labeling requirements and state common-law duties might otherwise leave drug manufacturers with conflicting obligations, § 314.70(c) allows manufacturers to avoid state failure-to-warn claims without violating federal law." App. 11a (citation omitted).

This expansive and result-oriented reading of the CBE regulation is clearly incompatible with FDA's overall regulatory labeling regime. As FDA explained in adopting the CBE provision in 1982, that regulation creates a limited exception to the general pre-approval regime to permit *newly discovered* information to be timely disseminated. *See* New Drug and Antibiotic Regulations, 47 Fed. Reg. 46,622, 46,623, 46,635 (Oct. 19, 1982) (codified at 21 C.F.R. pts. 310, 312, 314, 430, 431, 433); *see also Perry v. Novartis Pharma. Corp.*, 456 F. Supp. 2d 678, 682 (E.D. Pa. 2006) ("This particular regulation was promulgated precisely to allow drug-makers to quickly strengthen label warnings when evidence of *new* side effects are discovered." (emphasis added) (internal quotation marks and citation omitted)); *Weiss v. Fujisawa Pharm. Co.*, 464 F. Supp. 2d. 666, 675 (E.D. Ky. 2006) (explaining that a "drug manufacturer may warn patients and healthcare providers should they discover *new* evidence of a particular risk following the approval of the original label" (emphasis added)). While a "new information" trigger for using the CBE provision is not express in its text, it is necessarily implicit in FDA's larger regulatory scheme. *See* Labeling and Prescription Drug Advertising; Content and Format for Labeling for Human Prescription Drugs, 44 Fed. Reg. 37,434, 37,447 (June 26, 1979) (codified at 21 C.F.R. pts. 201-202); 71 Fed. Reg. at 3934, App. 128a-132a. FDA's comprehensive, particularized regulation of label formats and wording at the time of NDA approval cannot be reconciled with according manufacturers thereafter an unlimited ability to modify critical label language without prior FDA approval. *See Smith v. United States*, 508 U.S. 223, 234 (1993) ("A provision . . . is often clarified by the remainder of the statutory scheme . . .

because only one of the permissible meanings produces a substantive effect that is compatible with the rest of the law." (internal quotation marks and citation omitted)). In the words of Chief Justice Reiber, "the regulation does not allow manufacturers to simply reassess and draw different conclusions regarding the same risks and benefits already balanced by the FDA." App. 40a.

The facts of this case clearly show how the FDA regime can be disrupted by the CBE minimum standards approach. Here, the record unequivocally established that all information relating to the risks of IV injection of Phenergan put before the jury was available to FDA when it acted on Wyeth's supplemental NDA in 1997. The Vermont judicial process simply differed with FDA on the risk-benefit assessment appropriate to these facts, thus turning the CBE regulation into a recipe for balkanized and unbounded state second-guessing of federal regulatory actions. *See* App. 65a (calling FDA's regulatory process "slow and imperfect" and suggesting that FDA did not review "intravenous administration of Phenergan with scientific rigor or any sense of urgency").

This Court and the federal courts of appeal consistently have made clear that Congress has safeguarded FDA's science-based discretionary decisions from second-guessing in the federal courts, let alone fifty state courts. *See, e.g.*, *Heckler v. Chaney*, 470 U.S. 821, 835 (1985); *see also Weinberger v. Bentex Pharms., Inc.*, 412 U.S. 645, 653-54 (1973) ("The determination whether a drug is generally recognized as safe and effective . . . necessarily implicates complex chemical and pharmacological considerations" and is "peculiarly suited to initial determination by the FDA."); *Nutraceutical Corp. v. Von Eschenbach*, 459 F.3d 1033, 1043 (10th Cir. 2006) ("The review of scientific literature is properly in the province of the FDA, to which this Court grants deference based on its expertise."); *Schering Corp. v. FDA*, 51 F.3d 390, 399 (3d Cir. 1995) ("[FDA's] judgments as to what is required to ascertain the safety and efficacy of drugs fall squarely within the ambit of the FDA's expertise and merit deference from us.").

Distorting the CBE regulation to permit second-guessing by judges and juries in prescription drug injury cases, as occurred here,

is particularly pernicious. While FDA makes risk-benefit labeling decisions from a systemic, forward-looking perspective to optimize use of beneficial treatments, *supra* at 4, state judicial decisions make the same determinations "in hindsight through the lens of a single catastrophic case," App. 62a, and with an inevitable bias toward finding fault as a basis for compensation. Were manufacturers to label in response to, or in anticipation of, state determinations, they would be subject to myriad conflicting mandates, and numerous FDA judgments concerning optimal labeling and administrations of prescription drugs could be overridden, to the detriment of overall public health. *See Horn v. Thoratec Corp.*, 376 F.3d 163, 178 (3d Cir. 2004) (observing that excessive risk-oriented regulation "can harm the public health . . . by encouraging 'defensive labeling' by manufacturers to avoid state liability, resulting in scientifically unsubstantiated warnings and underutilization of beneficial treatments").

This Court should grant review to restore the integrity of FDA's regulatory regime in a "case in which the Federal Government has weighed the competing interests relevant to the particular requirement in question, reached an unambiguous conclusion about how those competing considerations should be resolved in a particular case or set of cases, and implemented that conclusion via a specific mandate on manufacturers or producers." *Medtronic Inc. v. Lohr*, 518 U.S. 470, 501 (1996). At least absent newly discovered scientific information permitting action under section 314.70(a), manufacturers like Wyeth should not be held liable for adhering to an FDA-approved label.

II. The Court Should Grant Review To Clarify the Effect, If Any, of the Presumption Against Preemption and Section 202 of the 1962 FDCA Amendments on the Application of "Obstacle" Conflict Preemption to Prescription Drug Cases.

Review also would allow the Court to articulate the analytical framework for applying conflict preemption principles

to the prescription drug regime when FDA's labeling regime permits manufacturers to initiate some modifications. Even if states have some authority to regulate such discretion as FDA affords to manufacturers, well-established principles of preemption forbid states from exercising that authority in a manner that would obstruct the objectives of federal law. *See McDermott v. Wisconsin*, 228 U.S. 115, 132 (1913) ("[T]o the extent that state law interferes with or frustrates the operation of the acts of Congress, its provisions must yield to the superior Federal power. . . ."). This Court has consistently made clear that conflict preemption analysis requires consideration *both* of whether it would be impossible to comply with federal and state law *and* of whether the state law would stand as an obstacle to the objectives of federal law:

> The Court has not previously driven a legal wedge – only a terminological one – between "conflicts" that prevent or frustrate the accomplishment of a federal objective and "conflicts" that make it "impossible" for private parties to comply with both state and federal law. Rather, it has said that both forms of conflicting state law are "nullified" by the Supremacy Clause, and it has assumed that Congress would not want either kind of conflict.

Geier, 529 U.S. at 873 (citations omitted).

The Vermont Supreme Court majority, however, simply declined to analyze obstacle preemption. The court determined that this line of inquiry was foreclosed by section 202 of the 1962 amendments to the FDCA, which it read as limiting the operation of preemption to cases in which it is *impossible* for a manufacturer to comply with both state and federal law. App. 22a ("[U]nder any circumstances where it is possible to comply with both state law and the FDCA, the state law in question is consistent with the purposes and objectives of Congress."). The majority attempted to bolster its conclusion by relying on a "presumption against preemption" of state regulatory powers in the area of public health. App. 23a-24a.

The majority's construction of section 202's "direct and positive" language is mistaken. This Court has made clear that the existence of such savings clauses specifically designed to protect the operation of state law does not preclude application of conflict preemption – including obstacle preemption. *See Geier*, 529 U.S. at 873-74 ("The Court has thus refused to read general "saving" provisions to tolerate actual conflict *both* in cases involving impossibility *and* in frustration-of-purpose cases. . . ." (internal quotation marks and citations omitted)). Instead of foreclosing conflict preemption, such provisions – within an otherwise comprehensive regulatory scheme – are best read to indicate Congress's intent merely to preclude field preemption – on which Wyeth does not rely. *See Schneidewind v. ANR Pipeline Co.*, 485 U.S. 293, 299-300 (1988).

That is precisely the effect of section 202. Because the 1962 FDCA amendments greatly expanded FDA's regulatory authority, there was legitimate concern that Congress might have been deemed to occupy the field of drug safety. The use of the phrase "direct and positive" was intended to preclude field preemption while fully preserving conflict preemption, nothing more. As the House sponsor of section 202 explained, this provision "would merely say that this Food and Drug Act shall not be construed as the intent of Congress to abolish *all State laws on the same subject where they are not in conflict with the Federal law.*" *See* 108 Cong. Rec. 21,083 (1962) (statement of Rep. Smith) (emphasis added). Indeed, courts determining whether a "direct and positive" conflict exists routinely conduct *both* an impossibility conflict *and* an obstacle conflict preemption analysis and make clear that this language operates only to bar field preemption. *See, e.g., Sinnot v. Davenport*, 63 U.S. (22 How.) 227, 242-43 (1859) (finding "direct and positive" conflict between federal and state law coasting trade provisions despite vessel owner's ability to comply with both and holding that "if this State law can be upheld, the full enjoyment of the right to carry on the coasting trade . . . is denied to the vessel in question"); *City of Camden v. Beretta U.S.A. Corp.*, 81 F. Supp. 2d 541, 549 (D.N.J. 2000) (finding that Gun Control Act's

"direct and positive conflict" phrase "compels a finding that the Gun Control Act only may be raised as an ordinary preemption defense to a conflicting state law, and not as a jurisdictional bar to all state claims relating to firearms" (internal quotation marks omitted)).[6]

The general presumption against preemption does not alter this result. The presumption is designed to ensure that "the historic police powers of the States were not to be superseded by the Federal Act unless that was the clear and manifest purpose of Congress." *Rice v. Santa Fe Elevator Corp.*, 331 U.S. 218, 230 (1947). Importantly, however, this presumption "is not triggered when the State regulates in an area where there has been a history of significant federal presence." *United States v. Locke*, 529 U.S. 89, 108 (2000); *see also Int'l Paper Co. v. Ouellette*, 479 U.S. 481, 491 (1987) ("[I]t is not necessary for a federal statute to provide explicitly that particular state laws are pre-empted."). In this regard, FDA has observed that "[i]n determining the proper role for state law in this context, . . . it is significant that the federal government has been regulating the manufacture and sale of drugs since 1906" – *i.e.*, for more than a century. Br. of the United States as Amicus Curiae in Support of Defendants-Appellees (filed Dec. 4, 2006), *Colacicco v. Apotex, Inc.*, No. 06-3107 (3d Cir.), at 17-18 n.7 ("Colacicco Br."). Granting review would enable this Court to make clear that state courts are not free simply to ignore this Court's settled "obstacle" conflict preemption doctrine through the overzealous application either of "direct and positive conflict" provisions or of the presumption against preemption.

The Vermont court should have examined whether the common law duty imposed on Wyeth posed an obstacle to FDA's

[6] This Court also has made clear that a federal statute's use of the term "provision" refers to positive enactments – not tort suit judgments. *See Cippollone v. Liggett Group, Inc.*, 505 U.S. 504, 518 (1992); *see also* Black's Law Dictionary 1262 (8th ed. 2004) (defining "provision" as "[a] clause in a statute, contract, or other legal instrument"). By its express terms, section 202 thus would not bar obstacle preemption even under the Vermont majority's misconstruction.

accomplishment of its congressionally mandated regulatory objectives. Under that analysis, the jury's verdict is preempted. As explained *supra* at 3, Congress specifically charged FDA with optimizing the use of prescription drugs by balancing their risks against their benefits to the overall public health. Permitting state tribunals to impose differing risk-benefit judgments on manufacturers, and to coerce labeling changes that FDA would not accept, would defeat congressional intent and lead to conflicting safety and warning standards imposed through the backward-looking lens of individual claims instead of the forward-looking public health determination that Congress mandated.

The facts of this case demonstrate why a state court's backward-looking, case-specific focus is inconsistent with FDA's broader regulatory perspective. FDA evaluated the risks associated with IV injection of Phenergan over a period of decades. Based on its scientific expertise, FDA determined that the efficacy benefits outweighed the risks and that physicians should retain the option to administer Phenergan via IV push, taking account of the extensive precautions and warnings in the approved label. App. 167a. FDA's determinations reflect its considered judgment that Phenergan's label reflected the correct risk-benefit balance and thus would render the drug of greatest benefit to the greatest number of people. *See United States v. Rutherford*, 442 U.S. 544, 555 (1979) ("[FDA] generally considers a drug safe when the expected therapeutic gain justifies the risk entailed by its use."). The Vermont Supreme Court would allow a jury to disagree with FDA's risk-benefit assessment and to override the federal regime by imposing a different labeling regime on Wyeth.

This is a paradigmatic case of state law frustrating the objectives and purposes of a federal regulatory regime by foreclosing a treatment option that the federal government has decided to hold open. As this Court made clear in *Geier*, such interference cannot survive constitutional scrutiny. In *Geier*, this Court held that a state common law duty to install airbags in all cars was preempted where federal regulation "deliberately

provided the manufacturer with a range of choices among different passive restraint devices." 529 U.S. at 875. *Geier* held that the state duty "would have presented an obstacle to the variety and mix of devices that the federal regulation sought" and "stood as an obstacle to the general passive restraint phase-in that the federal regulation deliberately imposed." *Id.* at 881; *see also Int'l Paper Co.*, 479 U.S. at 494 (striking down state law under conflict preemption that "upset[] the balance of public and private interests so carefully addressed by the [federal] Act"); *Buckman Co. v. Pls.' Legal Comm.*, 531 U.S. 341, 348 (2001) (observing that FDA uses its authority "to achieve a somewhat delicate balance of statutory objectives" and that this balance "can be skewed by allowing" state tort law claims that second-guess FDA's enforcement decisions).

Just as the petitioner in *Geier* could not use tort law to foreclose choices that the Department of Transportation deemed appropriate, Vermont here cannot be permitted to disturb the hierarchy of options for Phenergan administration that FDA repeatedly chose to preserve in Phenergan's labeling. This Court should grant certiorari and reverse the decision below so that lower courts will undertake the careful review necessary to determine whether compliance with a state-enforced duty, even if not expressly foreclosed by federal command, would, as here, obstruct rather than complement the objectives and purposes of FDA regulation.[7]

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[7] *Bates v. Dow Agrosciences LLC*, 544 U.S. 431 (2005), is fully consistent with this understanding. In *Bates*, this Court held that federal law did not expressly preempt "parallel" state law remedies for violation of federal misbranding law. *See* 544 U.S. at 449-51. Here, unlike *Bates*, Vermont common law seeks to provide litigants a cause of action separate and distinct from federal law; indeed, the Vermont courts made clear that Wyeth would be held liable irrespective of its fidelity to the federal labeling mandate. App. 28a. Accordingly, the reasoning that saved state "parallel requirements" from preemption is wholly inapposite here. The Vermont common law rule and FDA's labeling regime are not parallel.

III. The Court Should Grant Review To Resolve the Conflict Concerning the Degree of Deference that Courts Should Accord FDA's Formal Position on the Extent to Which State Tort Law Labeling Judgments Interfere with FDA's Labeling Regime.

Finally, this Court should grant review to resolve a lower court split on whether FDA's recently expressed judgments with respect to the adverse impact of state tort suits on its comprehensive prescription drug labeling regime are entitled to deference. In its preamble to an amended labeling regulation, FDA recently reiterated its longstanding view that suits such as this one obstruct its ability to ensure that prescribers receive accurate and helpful information about the proper uses of prescription drugs. *See* 71 Fed. Reg. at 3935, App. 132a-133a. The agency has explained why, in its expert judgment, additional labeling requirements imposed by state law may interfere with its ability to carry out its congressionally mandated function:

> State law actions . . . threaten FDA's statutorily prescribed role as the expert Federal agency responsible for evaluating and regulating drugs. State actions are not characterized by centralized expert evaluation of drug regulatory issues. Instead, they encourage, and in fact require, lay judges and juries to second-guess the assessment of benefits versus risks of a specific drug to the general public – the central role of FDA – sometimes on behalf of a single individual or group of individuals. That individualized reevaluation of the benefits and risks of a product can result in relief – including the threat of significant damage awards or penalties – that creates pressure on manufacturers to attempt to add warnings that FDA has neither approved nor found to be scientifically required. This could encourage manufacturers to propose "defensive labeling" to avoid State liability, which, if implemented,

> could result in scientifically unsubstantiated warnings and underutilization of beneficial treatments.

Id. at 3935.

This observation, based on FDA's expertise and experience, fully supports FDA's view that "[s]tate law conflicts with and stands as an obstacle to achievement of the full objectives and purposes of Federal law if it purports to preclude a firm from including in labeling . . . a statement that is included in [FDA-approved] prescription drug labeling." *Id.*; *see also id.* at 3934 ("FDA approval of labeling under the act, whether it be in the old or new format, preempts conflicting or contrary State law."). For all these reasons, FDA reiterated that it "interprets the act to establish both a 'floor' and a 'ceiling,' such that additional disclosures of risk information can expose a manufacturer to liability under the act if the additional statement is unsubstantiated or otherwise false or misleading." *Id.* at 3935.[8]

FDA expressed this same view in a number of recent amicus briefs. *See, e.g.*, Colacicco Br., *supra*; Letter Br. for FDA (filed Sept. 21, 2006), *Perry v. Novartis Pharms.*, No. 05-5350 (E.D. Pa.) ("Perry Br."). FDA explained therein that, "[i]n that context of drug labeling, Congress has authorized FDA to use scientific expertise to determine, in the first instance, what warnings are appropriate and necessary for a particular drug." Colacicco Br., *supra*, at 20. Moreover, "[i]f the agency had made a determination at a relevant time that a particular warning was unsubstantiated or would otherwise render the drug misbranded, then federal preemption bars liability for the failure to provide that warning." *Id.* at 23 n.10. Accordingly, "[e]ven if compliance with both state and federal law in these circumstances would not be impossible, state tort liability would pose a sufficient

[8] *See Hillsborough County v. Automated Med. Labs., Inc.*, 471 U.S. 707, 718 (1985) (confirming that agencies "can speak through a variety of means, including regulations, preambles, interpretive statements, and responses to comments"); *Fid. Fed. Sav. & Loan Ass'n v. de la Cuesta*, 458 U.S. 141, 158 (1982) (looking to regulatory preamble "for the administrative construction of the regulation, to which 'deference is . . . clearly in order'" (quoting *Udall v. Tallman*, 380 U.S. 1, 16 (1965)).

threat to federal regulatory objectives to be preempted under the Supremacy Clause." Perry Br., *supra*, at 10.[9]

According to the Vermont Supreme Court, "FDA's statement is neither an authoritative interpretation of an ambiguous statutory provision entitled to deference, nor a persuasive policy statement entitled to respect." App. 28a (internal citations omitted); *see also Jackson v. Pfizer, Inc.*, 432 F. Supp. 2d 964, 968 (D. Neb. 2006) ("The recent notice issued by the FDA claiming preemption is not persuasive."). In particular, the majority refused to credit FDA's conclusion that the "direct and positive" language of section 202 did not foreclose an analysis of state law interference with FDA's regulatory objectives. App. 135a, 21a.

Other courts have taken a different view of the importance of FDA's views on how state tort suits conflict with its regulatory regime and hamper its ability to do its job. *See In re Bextra*, 2006 WL 2374742, *6 ("The FDA's interpretation of the preemptive effect of its regulations is entitled to deference."); *Colacicco v. Apotex, Inc.*, 432 F. Supp. 2d 514, 525 (E.D. Pa. 2006) ("The FDA's view is critical to this Court's analysis because Supreme Court precedent dictates that an agency's interpretation of the statute and regulations it administers is entitled to deference."); *see also Horn*, 376 F.3d at 171 ("[T]he Supreme Court has instructed us that the FDA's preemption determinations are significant and should inform our interpretation . . . .").

This latter view is correct – FDA's substantive interpretation of its own regulations should be entitled to considerable deference – not the dismissive treatment given by the Vermont Supreme Court. *See Auer v. Robbins*, 519 U.S. 452, 461 (1997)

[9] *See Geier v. Am. Honda Motor Co.*, 529 U.S. 861, 883 (2000) (granting deference to the views expressed in an amicus brief submitted by the Solicitor General); *Auer v. Robbins*, 519 U.S. 452, 453 (1997) ("The Secretary's interpretation is not rendered unworthy of deference by the fact that it is set forth in an *amicus* brief; it is not a position adopted in response to litigation, and there is no reason to suspect that it does not reflect the Secretary's fair and considered judgment.").

(holding that an agency's interpretation of its regulations is "controlling unless plainly erroneous or inconsistent with the regulation" (internal quotation marks and citation omitted)). Similarly, FDA is best able to determine what interferes with its ability to fulfill its statutory mandate, and its views on that issue also merit substantial deference:

> Congress has delegated to [the agency] authority to implement the statute; the subject matter is technical; and the relevant history and background are complex and extensive. The agency is likely to have a thorough understanding of its own regulation and its objectives and is "uniquely qualified" to comprehend the likely impact of state requirements.

Geier, 529 U.S. at 883; *see also Thomas Jefferson Univ. v. Shalala*, 512 U.S. 504, 512 (1994) (finding that deference is especially warranted where agency decisions "require significant expertise and entail the exercise of judgment grounded in policy concerns" (internal quotation marks and citation omitted)).

Prescription drug labeling is precisely the type of complex and technical regulatory regime that warrants deference to the expertise of the agency that Congress charged with administering it. *See Bates v. Dow Agrosciences LLC*, 544 U.S. 431, 455 (2005) ("As suggested by *Medtronic*, the federal agency charged with administering the statute is often better able than are courts to determine the extent to which state liability rules mirror or distort federal requirements.") (Breyer, J., concurring). By disregarding FDA's interpretation of its own regulations and its views on the impact of state tort suits on the agency's regulatory objectives, the Vermont court committed a crucial error that infected its entire preemption analysis. The Court should grant review to correct this error and resolve this split in authority.

CONCLUSION

For the foregoing reasons, this Court should grant the petition for a writ of certiorari.

Respectfully submitted,

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APPENDIX

APPENDIX A — OPINION OF THE VERMONT SUPREME COURT FILED OCTOBER 27, 2006

SUPREME COURT

No. 2004-384

Diana Levine

v.

Wyeth

On Appeal from
Washington Superior Court

October Term, 2005

Geoffrey W. Crawford, J.

Richard I. Rubin and Kerry B. DeWolfe of Rubin, Kidney, Myer & DeWolfe, Barre, for Plaintiff-Appellee.

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Present: REIBER, C.J., DOOLEY and JOHNSON, JJ., and MORRIS, D.J., and ALLEN, C.J. (Ret.), Specially Assigned.

Appendix A

JOHNSON, J.

Defendant Wyeth, a drug manufacturer, appeals from a jury verdict in favor of plaintiff Diana Levine, who suffered severe injury and the amputation of her arm as a result of being injected with defendant's drug Phenergan. Plaintiff claimed at trial that defendant was negligent and failed to provide adequate warnings of the known dangers of injecting Phenergan directly into a patient's vein. Defendant argues that the trial court should not have allowed the jury to consider plaintiff's claims because the claims conflict with defendant's obligations under federal law regulating prescription drug labels. We hold that there is no conflict between state and federal law that requires preemption of plaintiff's claim. Defendant also raises two claims of error relating to the jury instructions on damages. We hold that the court's rulings on these jury instructions were correct, and we affirm.

In April 2000, plaintiff was injected with defendant's drug Phenergan at Northeast Washington County Community Health, Inc. ("the Health Center"). The drug was administered to treat plaintiff's nausea resulting from a migraine headache. Plaintiff received two injections. The drug was first administered by intramuscular injection. Later the same day, when plaintiff's nausea continued, she received a second dose by a direct intravenous injection into her arm, using a procedure known as "IV push." The second injection resulted in an inadvertent injection of Phenergan into an artery. As a result, the artery was severely damaged, causing gangrene. After several weeks of deterioration, plaintiff's hand and forearm were amputated.

Appendix A

Plaintiff brought a superior court action for negligence and failure-to-warn product liability, alleging that defendant's inadequate warning of the known dangers of direct intravenous injection of Phenergan caused her injuries. During a five-day jury trial, both parties presented expert testimony regarding the adequacy of the warnings defendant placed on Phenergan's label. Plaintiff's experts testified that the label should not have allowed IV push as a means of administration, as it was safer to use other available options, such as intramuscular injection or administration through the tubing of a hanging IV bag. Defendant's expert testified that allowing IV push with instructions cautioning against inadvertent arterial injection was sufficient. The court instructed the jurors that they could consider the FDA's approval of the label in use at the time of plaintiff's injury, but that the label's compliance with FDA requirements did not establish the adequacy of the warning or prevent defendant from adding to or strengthening the warning on the label. At the conclusion of the trial, the jury found in favor of plaintiff on both the negligence and product-liability claims and awarded her $2.4 million in economic damages and $5 million in non-economic damages. Pursuant to the parties' stipulation, this award was reduced to a total of $6,774,000 to account for pre-judgment interest and plaintiff's recovery in a settlement of a separate action she had filed against the Health Center.

In a summary judgment motion prior to trial, as well as in its timely motion for judgment as a matter of law following trial, both of which the superior court denied, defendant argued that federal law preempted plaintiff's claim. These arguments rested in part on defendant's contention that it

had submitted an adequate warning to the FDA, but that the FDA rejectedthe change because it did not favor strengthening the warning.[1] Plaintiff contended that neither warning would have been adequate. The trial court stated, in

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1. The warning on the label that was in use in 2000 read in relevant part:

INADVERTENT INTRA-ARTERIAL INJECTION: Due to the close proximity of arteries and veins in the areas most commonly used for intravenous injection, extreme care should be exercised to avoid perivascular extravasation or inadvertent intra-arterial injection. Reports compatible with inadvertent intra-arterial injection of [Phenergan], usually in conjunction with other drugs intended for intravenous use, suggest that pain, severe chemical irritation, severe spasm of distal vessels, and resultant gangrene requiring amputation are likely under such circumstances. Intravenous injection was intended in all the cases reported but perivascular extravasation or arterial placement of the needle is now suspect. There is no proven successful managemert of this condition after it occurs. . . .

When used intravenously [Phenergan] should be given in a concentration no greater than 25 mg per ml and at a rate not to exceed 25 mg per minute. WHEN ADMINISTERING ANY IRRITANT DRUG INTRAVENOUSLY IT IS USUALLY PREFERABLE TO INJECT IT THROUGH THE TUBING OF AN INTRAVENOUS INFUSION SET THAT IS KNOWN TO BE FUNCTIONING SATISFACTORILY.

(Emphasis added.) The revised warning the FDA failed to adopt read in relevant part:

INADVERTENT INTRA-ARTERIAL INJECTION: There are reports of necrosis leading to gangrene, requiring amputation, (Cont'd)

its decision on defendant's motion for judgment as a matter of law, that although the FDA had rejected a new warning, the agency's "brief comment" failed to explain its reasoning or demonstrate that it "gave more than passing attention to the issue of whether to use an IV infusion to administer the drug. The proposed labeling change did not address the use of a free-flowing IV bag." The court concluded that there was "no basis for federal preemption" and upheld the jury's verdict.

Defendant claims the superior court erred by: (1) failing to dismiss plaintiff's claim on the basis that the Food and Drug Administration's approval of the Phenergan label

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(Cont'd)
following injection of [Phenergan], usually in conjunction with other drugs; the intravenous route was intended in these cases, but arterial or partial arterial placement of the needle is now suspect. . . .

There is no established treatment other than prevention:

1. Beware of the close proximity of arteries and veins at commonly used injection sites and consider the possibility of aberrant arteries.

2. When used intravenously, [Phenergan] should be given in a concentration no greater than 25 mg/ml and a rate not to exceed 25 mg/minute. INJECTION THROUGH A PROPERLY RUNNING INTRAVENOUS INFUSION MAY ENHANCE THE POSSIBILITY OF DETECTING ARTERIAL PLACEMENT. IN ADDITION, THIS RESULTS IN DELIVERY OF A LOWER CONCENTRATION OF ANY ARTERIOLAR IRRITANT.

(Emphasis added.)

preempted state common law claims that the label was inadequate; (2) failing to instruct the jury to reduce plaintiff's damages by the amount of fault attributable to the Health Center; and (3) failing to instruct the jury to calculate the present value of plaintiff's damages for future non-economic losses. We reject these claims of error, and we affirm.

I. Federal Preemption

Defendant's principal argument on appeal is that the court should have dismissed plaintiff's claim because it was preempted by federal law. Defendant asserts that any state common law duty to provide a stronger warning about the dangers of administering Phenergan by IV push conflicts with the FDA's approval of the drug's label. As preemption is a question of law, we review the trial court's decision de novo. *Office of Child Support v. Sholan*, 172 Vt. 619, 620, 782 A.2d 1199, 1202 (2001) (mem.). We hold that the jury's verdict against defendant did not conflict with the FDA's labeling requirements for Phenergan because defendant could have warned against IV-push administration without prior FDA approval, and because federal labeling requirements create a floor, not a ceiling, for state regulation.

The United States Constitution provides that federal law is the supreme law of the land. U.S. Const. art. VI, cl. 2. The Supremacy Clause is the basis for the doctrine of preemption, according to which "state law that conflicts with federal law is 'without effect.'" *Cipollone v. Liggett Group, Inc.*, 505 U.S. 504, 516, 112 S.Ct. 2608, 120 L.Ed.2d 407 (1992) (quoting *Maryland v. Louisiana*, 451 U.S. 725, 746, 101 S.Ct. 2114, 68 L.Ed.2d 576 (1981)). In Cipollone, the Court

described the relevant analysis for determining whether Congress intended a federal statute to preempt state law:

> Congress' intent may be explicitly stated in the statute's language or implicitly contained in its structure and purpose. In the absence of an express congressional command, state law is pre-empted if that law actually conflicts with federal law, or if federal law so thoroughly occupies a legislative field as to make reasonable the inference that Congress left no room for the States to supplement it.

Id. (quotations and citations omitted). Absent clear congressional intent to supersede state law, including state common law duties, there is a presumption against preemption. *Medtronic, Inc. v. Lohr*, 518 U.S. 470, 485, 116 S.Ct. 2240, 135 L.Ed.2d 700 (1996) ("[B]ecause the States are independent sovereigns in our federal system, we have long presumed that Congress does not cavalierly pre-empt state-law causes of action."); *Cipollone*, 505 U.S. at 516 ("Consideration of issues arising under the Supremacy Clause 'start[s] with the assumption that the historic police powers of the States [are] not to be superseded by ... Federal Act unless that [is] the clear and manifest purpose of Congress.'" (quoting *Rice v. Santa Fe Elevator Corp.*, 331 U.S. 218, 230, 67 S.Ct. 1146, 91 L.Ed. 1447 (1947))). This presumption has "add[ed] force" when there has been a "long history of tort litigation" in the area of state common law at issue. *Bates v. Dow Agrosciences LLC*, 544 U.S. 431, 449, 125 S.Ct. 1788, 161 L.Ed.2d 687 (2005).

Appendix A

Defendant concedes that Congress has not expressly preempted state tort actions through the Food, Drug and Cosmetics Act (FDCA), 21 U.S.C. ¶ ¶ 301-399, and that Congress did not intend the FDCA to occupy the entire field of prescription drug regulation. Rather, it asserts that plaintiff's action "actually conflicts with federal law." *Cipollone*, 505 U.S. at 516. This requires defendant to show either that "it is impossible for a private party to comply with both state and federal requirements," or that Vermont's common law "stands as an obstacle to the accomplishment and execution of the full purposes and objectives of Congress." *Freightliner Corp. v. Myrick*, 514 U.S. 280, 287, 115 S.Ct. 1483, 131 L.Ed.2d 385 (1995) (quotations and citations omitted).

Defendant presents two alternative bases for its assertion of conflict preemption: (1) in the specific context of the Phenergan label, the FDA was aware of the dangers of IV-push administration and specifically ordered defendant to use the warning it used, making it impossible for defendant to comply with both its state common-law duty and the requirements of federal law; and (2) by penalizing drug companies for using FDA-approved wording on drug labels, state tort claims like plaintiff's present an obstacle to the purpose of the FDA's labeling regulations. Before reaching these issues, we briefly examine the FDA's role in regulating prescription drug labels and the general approach courts have taken to the preemptive effect of federal labeling requirements.

Appendix A

A. Regulatory Background

Prior to distributing a prescription drug such as Phenergan, the manufacturer must submit a New Drug Application (NDA) for FDA approval. 21 U.S.C. ¶ 355(a). The FDA must approve the application unless it fails to meet certain criteria, including whether test results and other information establish that the drug is "safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof," whether there is "substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling thereof," and whether, "based on a fair evaluation of all material facts, such labeling is false or misleading in any particular." *Id.* ¶ 355(d).

"FDA regulations mandate the general format and content of all sections of labels for all prescription drugs as well as the risk information each section must contain," and "[f]inal approval of the NDA is 'conditioned upon the applicant incorporating the specified labeling changes exactly as directed, and upon the applicant submitting to FDA a copy of the final printed label prior to marketing.'" *McNellis v. Pfizer, Inc.*, 2005 WL 3752269, at *4 (D.N.J.) (citing 21 C.F.R. ¶¶ 201.56, 201.57, and quoting 21 C.F.R. 314.105(b)). Once a drug and its label have been approved, any changes to the label ordinarily require submission and FDA approval of a "Supplemental NDA." *Id.*; 21 C.F.R. 314.70(b)(2)(v)(A).

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If the NDA process and the submission of changes for FDA approval were the exclusive means of creating and altering prescription drug labels, this might be a very different case. A key FDA regulation, however, allows a drug's manufacturer to alter the drug's label without prior FDA approval when necessary. The regulation provides in relevant part:

> (6) The agency may designate a category of changes for the purpose of providing that, in the case of a change in such category, the holder of an approved application may commence distribution of the drug product involved upon receipt by the agency of a supplement for the change. These changes include, but are not limited to:
>
> . . . .
>
> (iii) Changes in the labeling ... to accomplish any of the following:
>
> (A) To add or strengthen a contraindication, warning, precaution, or adverse reaction;
>
> . . . .
>
> (B) To add or strengthen an instruction about dosage and administration that is intended to increase the safe use of the drug product[.]

21 C.F.R. ¶ 314.70(c).

Appendix A

Section 314.70(c) creates a specific procedure allowing drug manufacturers to change labels that are insufficient to protect consumers, despite their approval by the FDA. "The FDA's approved label ... can therefore be said to set the minimum labeling requirement, and not necessarily the ultimate label where a manufacturer improves the label to promote greater safety." *McNellis*, 2005 WL 3752269, at *5. While specific federal labeling requirements and state common-law duties might otherwise leave drug manufacturers with conflicting obligations, ¶ 314.70(c) allows manufacturers to avoid state failure-to-warn claims without violating federal law. *Id.* ("[I]t is apparent that prior FDA approval need not be obtained, nor will a product be deemed mislabeled, if the manufacturer voluntarily or even unilaterally strengthens the approved warnings, precautions or potential adverse reactions upon the label pursuant to 21 C.F.R. ¶ 314.70(c)(6)(iii)(A)."). There is thus no conflict between federal labeling requirements and state failure-to-warn claims. Section 314.70(c) allows, and arguably encourages, manufacturers to add and strengthen warnings that, despite FDA approval, are insufficient to protect consumers. State tort claims simply give these manufacturers a concrete incentive to take this action as quickly as possible.

B. Conflict Preemption in Other Jurisdictions

In light of the leeway created by ¶ 314.70(c) for drug manufacturers to add warnings, courts have been nearly unanimous in holding that state failure-to-warn tort claims do not conflict with federal law. See, e.g., *McNellis*, 2005 WL 3752269, at *7 ("[T]he FDCA and the FDA's regulations do not conflict with New Jersey's failure to warn law because

those federal regulations merely set minimum standards with which manufacturers must comply."). McNellis is the latest in a series of recent cases addressing this issue as it relates to the anti-depressant *Zoloft*, which allegedly increases the risk of suicide in some patients. See id., at *7-8 (denying summary judgment and rejecting conflict preemption in *Zoloft* case); accord *Zikis v. Pfizer, Inc.*, 2005 WL 1126909, at *2-3 (N.D.Ill.); *Witczak v. Pfizer, Inc.*, 377 F.Supp.2d 726, 729-30 (D.Minn.2005); *Motus v. Pfizer, Inc.*, 127 F.Supp.2d 1085, 1096-1100 (C.D.Cal.2000); *see also Cartwright v. Pfizer, Inc.*, 369 F.Supp.2d 876, 882 (E.D. Tex. 2005) ("With little exception, courts that have considered this exact issue have concluded that state failure to warn claims are not preempted by the FDCA and its attendant regulations."). *Contra Needleman v. Pfizer, Inc.*, 2004 WL 1773697, at *1 (N.D. Tex.) (granting summary judgment to the defendant on basis of conflict preemption).

The Zoloft cases are representative of a general rule that FDA approval of a drug's label does not preempt state failure-to-warn claims. See, e.g., *Eve v. Sandoz Pharm. Corp.*, 2002 WL 181972, at *1-3 (S.D.Ind.) (rejecting conflict preemption of failure-to-warn claim regarding the drug Parlodel); *Caraker v. Sandoz Pharm. Corp.*, 172 F.Supp.2d 1018, 1032 (S.D.Ill.2001) (same); *Bryant v. Hoffman-La Roche, Inc.*, 262 Ga.App. 401, 585 S.E.2d 723, 725 (Ga.Ct.App.2003) (heart medication); *Bell v. Lollar*, 791 N.E.2d 849, 854-55 (Ind.Ct.App.2003) (prescription pain medication); *Kurer v. Parke, Davis & Co.*, 2004 WI App 74, 21, 272 Wis.2d 390, 679 N.W.2d 867 (oral contraceptive). But see *Ehlis v. Shire Richwood, Inc.*, 233 F.Supp.2d 1189, 1198 (D.N.D.2002) (granting summary judgment to defendant on basis of conflict preemption of claim regarding the drug Adderall).

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Defendant cites two cases, Needleman and Ehlis, that support the preemptive effect of the FDCA in failure-to-warn cases regarding prescription drug labels. *Needleman*, 2004 WL 1773697, at *1; *Ehlis*, 233 F.Supp.2d at 1198. Needleman is not particularly helpful under the circumstances here. Its holding relied on the facts of the *Zoloft* litigation, particularly an FDA statement that the warning advocated by the plaintiff would have been misleading. 2004 WL 1773697, at *1. The courts in the other Zoloft cases took a different approach to the FDA's statement, in part because the FDA's statement was not "an official agency position," and in part because the FDA later retracted its position regarding the link between *Zoloft* and suicide. See, e.g., *Witczak*, 377 F.Supp.2d at 730. Here, the FDA has not indicated that a stronger warning would be misleading, so the reasoning of Needleman appears inapplicable to this case. Ehlis interpreted ¶ 314.70(c) as allowing unapproved changes to a label only temporarily, and only under "limited circumstances." 233 F.Supp.2d at 1197-98. We can find no support for this interpretation in the language of the regulation, which appears to allow unilateral changes to drug labels whenever the manufacturer believes it will make the product safer, and places no limit on the duration of pre-approval warnings unless the FDA disapproves of the change. 21 C.F.R. ¶ 314.70(c).

Defendant next attempts to draw a comparison to the regulation of medical devices under the FDCA, citing medical device cases in which state tort law has been preempted. See *Buckman Co. v. Plaintiffs' Legal Comm.*, 531 U.S. 341, 348, 121 S.Ct. 1012, 148 L.Ed.2d 854 (2001) (holding that "fraud-on-the-FDA" claim relating to device regulated by Medical Device Amendments to FDCA was preempted); *Horn v.*

Thoratec Corp., 376 F.3d 163, 177 (3d Cir.2004) (holding that failure-to-warn claim was preempted by Medical Device Amendments). We find this analogy unpersuasive. Neither Buckman nor Horn weakens the force of the drug-labeling cases cited above. The claim that was preempted in Buckman was for "fraud on the FDA," not failure to warn; the Court held that the presumption against preemption applies only when a claim implicates "'the historic primacy of state regulation of health and safety,'" which is not the case when the claim arises from a federal statute. 531 U.S. at 347-48 (quoting *Medtronic*, 518 U.S. at 485). Plaintiff's negligence and product-liability claims fall squarely withn the scope of traditional state regulation, so it is appropriate to apply the presumption against preemption here. In Horn, the Third Circuit relied on an express preemption clause in the FDCA that relates only to medical devices. 376 F.3d at 176. Because no such clause exists for prescription drugs, Horn's reasoning does not apply to this case.

Finally, defendant cites a third group of cases relating generally to the United States Supreme Court's recent use of conflict preemption in other fields. This argument relies primarily on *Geier v. American Honda Motor Co.*, 529 U.S. 861, 120 S.Ct. 1913, 146 L.Ed.2d 914 (2000). In Geier, the Court held that state tort claims based on the production of automobiles without airbags conflicted with federal regulations making airbags one of several permissible safety equipment options. 529 U.S. at 881. Geier, however, rested on the conclusion that the Department of Transportation's intent in drafting the regulation at issue was to provide a range of different safety options, thus precluding any state determination that a specific type of equipment should be

required. *Id.* The history of the regulation at issue indicated that the agency intended to phase in automobile safety requirements gradually, allowing the public to choose between mandatory seatbelt laws at the state level and a federal passive-restraint requirement. *Id.* at 880-81. Allowing state tort claims based on the lack of a particular safety mechanism would have conflicted with both the agency's phase-in plan and its intent to provide consumers with a range of safety options. *Id.* at 881. The Court explicitly stated that in a different context, an agency could promulgate regulations that provided a floor, but not a ceiling, for state regulation. *Id.* at 870.

The FDA's labeling requirements are exactly that type of regulation. Section 314.70(c) does not allow us to interpret FDA approval of a drug label as anything but a first step in the process of warning consumers. When further warnings become necessary, the manufacturer is at least partially responsible for taking additional action, and if it fails to do so, it cannot rely on the FDA's continued approval of its labels as a shield against state tort liability. While a state common-law duty may encourage departure from a label that the FDA has approved in great detail, such a duty does not create a conflict with federal requirements because the FDA and the state share the purpose of encouraging pharmaceutical companies to alter their drug labels when they are inadequate to protect consumers. We agree with the significant majority of courts that state failure-to-warn claims are generally not preempted by federal labeling requirements.

We must now apply this reasoning to defendant's two original contentions: (1) notwithstanding the fact that it is generally possible for manufacturers to comply with both federal and state law through the procedures created by ¶ 314.70(c), the FDA's specific actions with respect to *Phenergan* made it impossible for defendant to comply with both federal and state law; and (2) even if plaintiff's claim and the cases cited above do not make it impossible for manufacturers to comply with both state and federal law, they present an obstacle to federal objectives.

C. Impossibility of Compliance

Defendant contends that in this case, it was impossible to comply with both state and federal law because the FDA prohibited the use of a stronger warning with respect to IV-push administration of Phenergan. This claim is not supported by the evidence defendant presented to the trial court. The record lacks any evidence that the FDA was concerned that a stronger warning was not supported by the facts, that such a stronger warning would distract doctors from other provisions in the drug's label, or that the warning might lead to less effective administration of the drug. Instead, defendant essentially relies on two factual assertions: 1) the FDA approved the label that was in use in 2000; and 2) the FDA, in reviewing the label for use in a different version of Phenergan, expressed its opinion of the adequacy of the warning in the original label by stating, "Retain verbiage in current label." AB 5, 5 n. 7

With respect to defendant's first assertion, our analysis above demonstrates that FDA approval of a particular label does not preempt a jury finding that the label provided insufficient warning, as defendant was free under ¶ 314.70(c) to strengthen the warning without prior FDA approval. Defendant's second assertion depends on the meaning of the instruction, "[r]etain verbiage in current label." Tort liability for defendant's failure to strengthen its warningcould have created a direct conflict requiring federal preemption only if the FDA intended the instruction to prohibit any language strengthening the original warning. In other words, unless we interpret the FDA's statement as evidence that it would have rejected any attempt by defendant to strengthen its label through ¶ 314.70(c), we cannot conclude that it was impossible for defendant to comply with its state common-law duty without violating federal law.

Defendant argues that the instruction reflected the FDA's opinion not only that a stronger warning was unnecessary, but also that it would have harmed patients by eliminating IV push as an option for administering *Phenergan*. The record does not support this interpretation. Defendant has provided a number of letters exchanged by the FDA and defendant regarding Phenergan's label, but these letters do not indicate the FDA's opinion of the value of IV-push administration. Neither the letters nor any other evidence presented to the jury indicated that the FDA wished to preserve the use of IV push as a method of administering Phenergan. Nor can we infer such concern from the agency's instruction to "[r]etain current verbiage" instead of adopting the proposed warning. The specific warning the agency rejected in favor of the original label did not indicate any more clearly than the

original label that IV-push administration was unsafe, which is what plaintiff argued made the original label inadequate. The FDA could have rejected the new warning for any number of reasons, including clarity or technical accuracy, without implicitly prohibiting a stronger warning. Defendant's unsupported hypothesis that the FDA saw the new warning as harmful seems among the least likely explanations, as the rejected proposal would not have eliminated IV push as an option for administering Phenergan.[2] With respect to IV administration, the original label read, "When administering any irritant drug intravenously it is usually preferable to inject it through the tubing of an intravenous infusion set that is known to be functioning satisfactorily," while the proposed label stated, "[i]njection through a properly running intravenous infusion may enhance the possibility of detecting arterial placement. In addition, this results in delivery of a lower concentration of any arteriolar irritant." See supra 4 n. 1 (comparing proposed and original warnings). Simply stated, the proposed warning was different, but not stronger. It was

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2. The dissent appears to interpret any warning that would eliminate IV-push administration as inherently inconsistent with the FDA's approval of Phenergan for IV administration in general. We see no such inconsistency, as an approval of a drug for IV administration is not the same as a conclusion that all methods of IV administration are safe. In any case, a jury verdict in a failure-to-warn case simply establishes that the relevant warning was insufficient; it does not mandate a particular replacment warning. There may have been any number of ways for defendant to strengthen the Phenergan warning without completely eliminating IV-push administration. Our purpose in pointing out that the proposed warning the FDA rejected did not eliminate IV push is simply that rejecting this warning could not be seen as an affirmative effort by the FDA to preserve IV push as an option.

also no longer or more prominent than the original warning, so it could not have raised a concern that it might overshadow other warnings on the label or drive doctors away from prescribing the drug. There is no evidence that the FDA intended to prohibit defendant from strengthening the *Phenergan* label pursuant to ¶ 314.70(c).[3] Thus, we cannot conclude that it was impossible for defendant to comply with its obligations under both state and federal law.

D. Obstacle to Congressional Purposes and Objectives

Defendant next contends that state common-law liability for its use of an FDA-approved label presents an obstacle to federal objectives. We hold that plaintiff's claim does not interfere with any objective that can legitimately be ascribed to Congress. We agree with the reasoning in the cases cited above, supra 14-15, that federal labeling requirements pursuant to the FDCA create a floor, not a ceiling, for state regulation. Defendant presents a new FDA rule containing language disputing this reasoning, but this statement does not alter our conclusion that there is no conflict between federal objectives and Vermont common law.

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3. We also reject defendant's argument that it would have been prosecuted for "misbranding" if it had strengthened the label without prior approval. See *Witczak*, 377 F.Supp.2d at 731, 729 ("[T]he validity and authority of state law ... does not depend on speculative hypotheticals" regarding "assumptions of what the FDA would have done" in response to a stronger warning.).

Appendix A

1. The Purposes and Objectives of Congress

In the absence of a conflict that makes it impossible for a regulated entity to comply with both state and federal law, federal law will preempt state law only if it "stands as an obstacle to the accomplishment and execution of the full purposes and objectives of Congress." *Freightliner*, 514 U.S. at 287 (quotations omitted). We must therefore examine what "the full purposes and objectives of Congress" were with respect to federal labeling requirements for prescription drugs. We agree with the McNellis court that a system under which "federal regulations merely set minimum standards with which manufacturers must comply" is

> fully consistent with Congress' primary goal in enacting the FDCA, which is "to protect consumers from dangerous products," *United States v. Sullivan*, 332 U.S. 689, 696, 68 S.Ct. 331, 92 L.Ed. 297 (1948), as well as Congress' stated intent that the FDCA "'must not weaken the existing laws,' but on the contrary 'it must strengthen and extend that law's protection of the consumer.'" *United States v. Dotterweich*, 320 U.S. 277[, 282] (1943) [quoting S.Rep. No. 152, 75th Cong., 1st Sess., p. 1].

2005 WL 3752269, at *7; *see also Witczak*, 377 F.Supp.2d at 731 ("Congress certainly did not intend to bar drug companies from protecting the public when enacting the FDCA; its goal was to protect the public.... Any contrary interpretation of Congress's intent is perverse.").

In fact, Congress has expressed its purposes clearly, not only in the general sense that the statute was intended to "protect the public," but also more specifically, with respect to the FDCA's preemptive effect. In the 1962 amendments to the FDCA, Congress included a clause expressly limiting the preemptive effect of the statute: "Nothing in the amendments made by this Act to the Federal Food, Drug, and Cosmetic Act shall be construed as invalidating any provision of State law ... unless there is a direct and positive conflict between such amendments and such provision of State law." Drug Amendments of 1962 (Harris Kefauver Act), Pub.L. No. 87 781, ¶ 202, 76 Stat. 780, 793 (1962).

This amendment essentially removes from our consideration the question of whether common-law tort claims present an obstacle to the purposes and objectives of Congress. Congress intended that the FDCA would leave state law in place except where it created a "direct and positive conflict" between state and federal law. Drug Amendments ¶ 202. This language "simply restates the principle that state law is superseded in cases of an actual conflict with federal law such that 'compliance with both federal and state regulations is a physical impossibility.'" See *S. Blasting Servs., Inc. v. Wilkes County*, 288 F.3d 584, 591 (4th Cir.2002) (interpreting "direct and positive conflict" language in the preemption clause of a federal statute governing explosive materials to allow states to "impose more stringent requirements than those contained in the federal regulations") (quoting *Hillsborough County v. Automated Med. Labs., Inc.*, 471 U.S. 707, 713, 105 S.Ct.

2371, 85 L.Ed.2d 714 (1985)).[4] In other words, under any circumstances where it is possible to comply with both state law and the FDCA, the state law in question is consistent with the purposes and objectives of Congress. Thus, our

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4. The debate surrounding the amendment helps confirm that it was intended to preserve the right of states to regulate beyond the federal requirements of the FDCA. During the floor debate in the House, the subject of preemption arose several times. First, Congressman Smith of California expressed concern that the bill, as reported, contained "no language ... which says anything to the effect that this particular measure will not preempt all State food and drug laws," and thus, might risk interfering with the efforts of some states to make their own, stricter regulations. 108 Cong. Rec. 21046 (1962) ("[I]t seems to me that if we are going to pass this law, someone ought to offer an amendment to make certain that the passage of this bill, which gives all of this power to the Department of Health, Education, and Welfare and the Food and Drug Administration, will not preempt any State laws"). Shortly thereafter, Congressman Harris of Arkansas, the primary House sponsor of the bill, offered his opinion that "there is nothing in this bill that in any way preempts the authority and prerogatives of the States." *Id.* at 21047. Congressman Schenck of Ohio agreed, stating, "[m]any very helpful State laws are in effect; many such laws in some instances are even stronger than Federal laws for the protection of human health in the public interest." *Id.* at 21056.

Congressmen Schenck and Harris, despite insisting that the bill as written would not preempt stronger state laws, eventually supported the "direct and positive conflict" amendment, and Schenck reiterated that preemption should not apply in the "many instances where State laws in the area of food and drugs and health are even stronger than some of the Federal laws." *Id.* at 21083. Neither the desirability of allowing states to regulate beyond the FDCA nor the intent of the amendment to protect such regulation from preemption was called into question during the debate.

discussion above regarding defendant's impossibility argument, supra 21-23, provides a complete answer to the question of preemption.

We recognize that our dissenting colleague has reached the opposite conclusion. There is little to say, beyond what we have already said, except that we respectfully disagree with his analysis of the FDCA, the FDA's regulations, and the specific context of this lawsuit. Numerous courts have concluded, over the course of decades, that the FDCA provides a floor, not a ceiling, for state regulation. See supra, 14-15. While the dissent cites favorably the minority view, we agree with the majority view. There is much to be said for the policy arguments employed by courts adopting this minority view, including the argument that permitting too much state activity in this area will make beneficial drugs less available to consumers. Similarly, there is merit to the majority perspective that eliminating lawsuits like the one at issue here would leave consumers without recourse in the event the FDA cannot move quickly enough to require strengthened warnings when they are appropriate. Our view is that neither policy argument is relevant here. The plain language of the statute indicates that Congress did not intend to interfere with state prerogatives except where doing so is absolutely necessary, see supra, 25-27, and the plain language of the regulation makes such interference unnecessary here, see supra, 12-13. This analysis is consistent with the constitutionally rooted presumption against preemption. To look more broadly at arguments relying on assumptions about safety and economic efficiency is to apply the opposite presumption-the presumption that Congress could not possibly have intended to allow states to intrude on what

seems, intuitively, to be an area of federal expertise. It is neither our responsibility, nor that of the FDA, to question the policy judgments of Congress. The litigation at issue here does not pose a direct and positive conflict with federal law, and thus, there is no basis for federal preemption.

2. The FDA's New Statement on Preemption

Defendant, after oral argument in this case, cited a new FDA regulation that contains a statement relating to the preemptive effect of the FDCA. The substance of the regulation changes certain aspects of labeling requirements for prescription drugs, but these changes are irrelevant to this appeal because the new rule did not take effect until June 2006. Food and Drug Administation, *Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products, Supplementary Information,* 71 Fed.Reg. 3922, 3922 (Jan. 24, 2006). The rule's "Supplementary Information" section, however, contains a broad statement regarding the preemption of state common-law failure-to-warn claims. *Id.* at 3933-36. In this statement, the FDA asserts that recent cases rejecting preemption of these claims, including those cited above, pose an obstacle to the agency's enforcement of the labeling requirements. Id. Among the interpretations the agency claims are incorrect are: (1) those rejecting preemption on the basis of ¶ 314.70(c); and (2) those stating that federal labeling requirements are minimum standards and that "[s]tate law serves as an appropriate source of supplementary safety regulation for drugs by encouraging or requiring manufacturers to disseminate risk information beyond that required by FDA under the act." *Id.* at 3934.

We are ordinarily required to defer to an agency's interpretation of a statute it administers. *Chevron, U.S.A., Inc. v. Natural Res. Def. Council*, 467 U.S. 837, 844, 104 S.Ct. 2778, 81 L.Ed.2d 694 (1984) ("We have long recognized that considerable weight should be accorded to an executive department's construction of a statutory scheme it is entrusted to administer...."). Plaintiff, however, urges us not to defer to the FDA's statement because it "was adopted without the requisite comment period" and "lack[s] the force of law." Presumably, if we were to credit plaintiff's argument, we would owe the statement only the limited deference due to agency statements made outside the agency's rulemaking authority. See *United States v. Mead Corp.*, 533 U.S. 218, 226-27, 121 S.Ct. 2164, 150 L.Ed.2d 292 (2001) (stating that Chevron deference applies only "when it appears that Congress delegated authority to the agency generally to make rules carrying the force of law, and that the agency interpretation claiming deference was promulgated in the exercise of that authority"). We need not decide this difficult question of administrative law, however, because we conclude that irrespective of the level of deference we might apply, the statement would not affect the outcome of this appeal.

Under Chevron, deference to an agency's interpretation is appropriate only when a statute is "silent or ambiguous with respect to the specific issue" the agency has considered; otherwise, "the court, as well as the agency, must give effect to the unambiguously expressed intent of Congress." 467 U.S. at 842-43. Moreover, "[t]he judiciary is the final authority on issues of statutory construction and must reject administrative constructions which are contrary to clear

congressional intent." *Id.* at 843 n. 9. "If a court, employing traditional tools of statutory construction, ascertains that Congress had an intention on the precise question at issue, that intention is the law and must be given effect." *Id.* When an agency's interpretation is not the type of interpretation entitled to Chevron deference, we must still grant it some respect, but only "a respect proportional to its 'power to persuade.'" *Mead*, 533 U.S. at 235 (quoting *Skidmore v. Swift & Co.*, 323 U.S. 134, 140, 65 S.Ct. 161, 89 L.Ed. 124 (1944)).

Under either standard, the FDA's statement deserves no deference. We have already concluded, supra 26-27, that Congress intended the FDCA to preempt only those state laws that would make it impossible for manufacturers to comply with both federal and state requirements. Nothing in the FDA's new statement alters our conclusion that it would be possible for defendant to comply with both its federal obligations and the obligations of state common law. The regulatory framework for prescription drug labeling allows drug manufacturers to add or strengthen a warning "to increase the safe use of the drug product" without prior FDA approval. See supra 10-13 (citing 21 C.F.R. ¶ 314.70(c)(6)(iii)(C)). Even if the new rule eliminated or altered this provision, the change in the regulation did not take effect until June 2006.[5] Without such a change, it is possible for manufacturers to comply with both FDA regulations and duties imposed by state common law, and there is no "direct and positive conflict" between state and federal law.

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5. The only alteration the new rule appears to make to ¶ 314.70 is that changes to the new "Highlights" section of a drug label may not be made without prior approval. 71 Fed.Reg. at 3934.

The FDA does not attempt to establish such a conflict or explain the inconsistency between its position and the language of the preemption amendment. The statement cites the amendment, but then proceeds as if Congress had not spoken on the issue of preemption. The agency relies on Geier to support its disregard of Congress's "direct and positive conflict" language, asserting that "[t]he existence of a legislative provision addressing pre-emption does not bar the operation ofordinary principles of implied preemption." 71 Fed.Reg. at 3935 (citing *Geier*, 529 U.S. at 869). Geier does state that implied preemption applies even when a statute addresses preemption expressly, 521 U.S. at 869, but it does not allow courts or agencies to preempt state laws that have been expressly preserved by Congress. Instead, it simply stands for the proposition that Congress's intent not to preempt a provision of state law cannot be inferred from either (1) an express preemption clause that does not include the state law in question in its scope, or (2) a clause that prevents regulated entities from using compliance with federal law as a defense in state common-law suits. *Id.* at 869-70. According to Geier, the former clause does not support a negative inference that Congress must have intended to preserve laws it did not expressly preempt; the latter indicates only that Congress intended to preserve some common-law claims, not that it intended to allow even claims that conflict with federal requirements. *Id.* But see id. at 870 (stating that even the latter clause would "preserve [ ] those actions that seek to establish greater safety than the minimum safety achieved by a federal regulation intended to provide a floor").

Here, we are not attempting to infer the effect of statutory language that only indirectly addresses the specific state law at issue. Instead, we are interpreting an unambiguous express preemption clause that specifically preserves the type of state law at issue. Under these circumstances, ordinary preemption principles must give way to Congress's intent to preserve state laws that do not create a "direct and positive conflict" with federal law. Drug Amendments ¶ 202. There is no such conflict here. Accordingly, the FDA's statement is neither an authoritative interpretation of an ambiguous statutory provision entitled to deference, *Chevron*, 467 U.S. at 842-43, nor a persuasive policy statement entitled to respect. *Mead*, 533 U.S. at 235. Plaintiff's claim does not impose conflicting obligations on defendant or present an obstacle to the objectives of Congress. We therefore agree with the trial court that the claim is not preempted by federal law.

II. Apportionment of Damages

Defendant next contends the court erred by failing to instruct the jury to reduce plaintiff's damages by the amount of fault attributable to the Health Center. "Reversing a jury verdict based on allegedly faulty jury instructions is warranted where the party claiming error establishes that the instructions were erroneous and prejudicial." *Simpson v. Rood*, 2005 VT 21, 5, 178 Vt. 474, 872 A.2d 306 (mem.). We hold that there was no error in the court's failure to require apportionment of damages between defendant and the Health Center.

Defendant argues that pursuant to Vermont's comparative negligence statute, a defendant is liable for only the portion of the plaintiff's damages attributable directly to that

defendant's negligence. 12 V.S.A. ¶ 1036. Our traditional rule is that multiple tortfeasors are jointly and severally liable. See *Zaleskie v. Joyce*, 133 Vt. 150, 158, 333 A.2d 110, 115 (1975) ("[T]he law of this state ... permits a plaintiff to pursue all, or any part, of his recovery from either joint tortfeasor"). According to defendant, ¶ 1036 applies not only under circumstances where comparative negligence is alleged on the part of the plaintiff, and not only when multiple defendants are sued in the same action, but also any time the plaintiff recovers from someone besides the defendant. Thus, because plaintiff and the Health Center reached a settlement in a separate lawsuit related to the same injury, defendant claims the jury should have been required to calculate the Health Center's proportion of causal negligence and subtract that percentage from the verdict.

Section 1036 states, under the heading of "Comparative negligence,"

> Contributory negligence shall not bar recovery in an action by any plaintiff, or his legal representative, to recover damages for negligence resulting in death, personal injury or property damage, if the negligence was not greater than the causal total negligence of the defendant or defendants, but the damage shall be diminished by general verdict in proportion to the amount of negligence attributed to the plaintiff. Where recovery is allowed against more than one defendant, each defendant shall be liable for that proportion of the total dollar amount awarded as damages in the ratio of the amount of his causal

> negligence to the amount of causal negligence attributed to all defendants against whom recovery is allowed.

12 V.S.A. ¶ 1036. We interpreted this statute under slightly different circumstances in *Plante v. Johnson*, 152 Vt. 270, 565 A.2d 1346 (1989). In Plante, the defendant resisted joinder of the plaintiffs' claims against her and a third party, resulting in a joint trial with two separate verdicts. The jury first returned a verdict against the third party for the entire amount of the plaintiff's damages, then found against the defendant for the same amount, and the court consolidated the judgments. The defendant appealed, arguing that the first verdict made the third party's share of the fault 100%. She concluded that under ¶ 1036, she was entitled to a ruling apportioning 100% of the liability for the plaintiff's damages to the third party. The defendant failed to argue this point at trial, making a holding regarding ¶ 1036 unnecessary. We nevertheless examined the statute in depth to demonstrate that our determination that the defendant was not entitled to apportionment was "more than a technical omission." *Id. at* 272, 565 A.2d at 1347. We concluded that the statute did not apply to the defendant in Plante because "the statute provides for apportionment among defendants, suggesting that only those joined in the same action should be considered in apportioning damages," and "there is no allegation that the plaintiff was negligent in this case."[6] *Id.* at 273, 565 A.2d at 1347-48.

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6. We also listed as an additional reason, not applicable here, that the third party whose liability was at issue in Plante was held liable under a different theory of liability that was not clearly within the scope of ¶ 1036. Id. at 273, 565 A.2d at 1348.

In reaching this conclusion, we relied in part on the fact that "the New Hampshire Supreme Court has held that its nearly identical statute does not apply to create several liability in the absence of an allegation of negligence on the part of the plaintiff." *Id.*, 565 A.2d at 1348 (citing *Lavoie v. Hollinracke*, 127 N.H. 764, 513 A.2d 316, 319-20 (N.H.1986)). Defendant points out that Lavoie has since been overruled, but the decision overruling it, *Nilsson v. Bierman*, 150 N.H. 393, 839 A.2d 25 (N.H.2003), relied on a legislative revision of New Hampshire's statute that placed the concepts of comparative negligence and apportionment under separate headings. *Id.* at 29. In the absence of action by the Legislature to amend Vermont's comparative negligence statute, we see no reason to depart from the interpretation of ¶ 1036 contained in Plante. The Health Center was not a party to plaintiff's action against defendant, and defendant does not allege that plaintiff was comparatively negligent, so ¶ 1036 does not apply in this case.

Defendant argues that whether or not ¶ 1036 applies, we can depart from our common law and determine that joint and several liability should no longer prevent apportionment among joint tortfeasors when one tortfeasor has settled in a previous action. We decline to do so. In *Howard v. Spafford*, 132 Vt. 434, 321 A.2d 74 (1974), which also involved an interpretation of ¶ 1036, we expressed our hesitation to depart from the rule precluding contribution among joint tortfeasors, preferring not to "substitute judicial fiat for legislative action." *Id.* at 435, 321 A.2d at 75. Among the many reasons cited in Howard for adhering to the common law was the sheer number of alternative schemes adopted by other states. *Id.* at 436-37, 321 A.2d at 75-76. This reasoning applies here

as well. Our choice is not between the traditional rule and a uniform new rule, but rather between a traditional rule and a number of potential new rules or combinations of rules. The Nilsson court pointed out the divide among states requiring jury verdicts to be reduced by the dollar amount of the plaintiff's settlement with a third party (pro tanto), those requiring verdicts to be reduced by the percentage of the settling party's fault (proportional share), and those requiring verdicts to be divided among all joint tortfeasors equally (pro rata). 839 A.2d 30-31. That court pointed out that while "[t]he American Law Institute favors the proportional share approach ..., the overwhelming majority of States reject the proportional share approach in favor of some version of the pro tanto approach," and New Hampshire's legislature chose a combination of the two. Id. at 31 (citations and quotations omitted). It is important to note that if we were to adopt the majority rule, our decision would have no effect on this case, as plaintiff and defendant have stipulated to a pro tanto reduction. Like the New Hampshire court, we will allow the Legislature to determine which approach is best, if it has not done so already by leaving ¶ 1036 in place after our interpretation in Plante.

III. Present Value of Damages

Finally, defendant contends the court erred by failing to instruct the jury to calculate the present vale of plaintiff's damages for future non-economic losses, such as pain and suffering. Defendant claims that the jury's verdict, which granted plaintiff $5 million in non-economic damages, exceeded the present value of plaintiff's requested amount by $856,073. In rejecting defendant's proposed instruction,

the court pointed out that defendant failed to provide the jury with expert guidance as to how present value should be calculated, and that "[j]udges and lawyers are universally incapable of performing the discount calculations with or without a calculator and the tables of historic interest rates and inflationary factors." We agree that it would have been inappropriate to instruct the jury to make such a calculation under these circumstances.

Even if defendant had presented testimony allowing the jury to make an informed calculation, we would have upheld the jury's verdict for several reasons. First, defendant's assertion that the jury did not take account of the present value of plaintiff's non-economic damages is pure speculation, as plaintiff's calculation of her economic damages was presented in terms of its present value, and "the jury was not required to demonstrate its calculations" with respect to plaintiff's non-economic damages. *Debus v. Grand Union Stores of Vt.*, 159 Vt. 537, 543, 621 A.2d 1288, 1292 (1993). Second, we limit pre-judgment interest to economic damages because non-economic damages are "inchoate and rarely ascertainable at the time of injury." *Turcotte v. Estate of LaRose*, 153 Vt. 196, 200 n. 2, 569 A.2d 1086, 1088 n. 2 (1989). These damages become no less inchoate following a judgment, and we will not require juries to apply a precise economic calculation to a figure we have identified as inherently imprecise.

Finally, most jurisdictions and the Restatement (Second) of Torts reject the concept of requiring juries to make present-value calculations with respect to non-economic damages. See, e.g., *Taylor v. Denver & Rio Grande W. R.R.*, 438 F.2d

351, 353 (10th Cir.1971) (holding that instruction requiring present-value reduction for pain and suffering was error and stating that most courts that have considered the issue have decided "that the better reasoned authority supports the rule that future pain and suffering should not be reduced to current worth"); Restatement (Second) of Torts ¶ 913A cmt. a (1979) (stating that while future pecuniary losses should be reduced to present value, "an award for future pain and suffering or for emotional distress is not discounted in this fashion"). But see *Olivieri v. Delta S.S. Lines, Inc.*, 849 F.2d 742, 750-51 (2d Cir.1988) (stating that "[i]f we were writing on a clean slate, we might be inclined to accept the view of the other circuits and reject any discounting of future non pecuniary losses," but previous Second Circuit holdings required such discounting in some form). Defendant's reliance on our decision in *Parker v. Roberts*, 99 Vt. 219, 131 A.2d 21 (1925), is misplaced, as Parker, while it required a jury instruction on the present value of future losses, did not address the distinction between pecuniary and non-pecuniary losses. *Id.* at 224-25, 131 A. 21, 131 A.2d at 23. The trial court did not err in refusing to instruct the jury to reduce plaintiff's non-economic damages to present value.

Affirmed.

Associate Justice

Appendix A

Dissenting

REIBER, C.J., dissenting. The overarching issue in this appeal is whether plaintiff's common-law claim for failure to warn conflicts with the FDA's regulation of Phenergan, the drug responsible for plaintiff's injuries. I would conclude that the jury's verdict in this case conflicts with federal law for two reasons.

First, it would be impossible for defendant Wyeth to comply with the requirements of both state and federal law. Specifically, the FDA approved IV administration of Phenergan and required that IV administration be listed on the Phenergan label. By contrast, plaintiff's theory of the case required Wyeth either to remove this approved use from the Phenergan label, add a warning that would directly contradict the label's indication that IV administration was a safe and effective use, or, at a minimum, add a warning that only certain types of IV administration should be used. Thus, compliance with state law in this case would require Wyeth to eliminate uses of Phenergan approved by the FDA and required to be included in the Phenergan labeling.

Second, plaintiff's state-law claim conflicts with federal law in that it poses an obstacle to federal purposes and objectives. In short, by approving Phenergan for marketing and distribution, the FDA concluded that the drug-with its approved methods of administration and as labeled-was both safe and effective. See 21 U.S.C. ¶ 355(d) (listing criteria for drug approval). In finding defendant liable for failure to warn, a Vermont jury concluded that the same drug-with its approved methods of administration and as labeled-was "unreasonably dangerous." See *Town of Bridport v. Sterling*

Clark Lurton Corp., 166 Vt. 304, 308, 693 A.2d 701, 704 (1997) (to succeed on failure-to-warn claim, plaintiff must show that "failure to warn made the product unreasonably dangerous and therefore defective"). These two conclusions are in direct conflict.

For both of these reasons I would conclude that the state-law cause of action is preempted. I respectfully dissent.

I. Impossibility of Compliance

As explained by the majority, because there is no clause in the FDCA expressly preempting state law, Wyeth must demonstrate that preemption is implied by showing either that federal law thoroughly occupies the regulatory field (a claim that Wyeth does not advance) or that there is an actual conflict between state and federal law. Actual conflict, in turn, can be demonstrated in one of two ways: by showing that it is impossible for the regulated party to comply with both state and federal law or that state law "stands as an obstacle to the accomplishment and execution of the full purposes and objectives of Congress." *Freightliner Corp. v. Myrick*, 514 U.S. 280, 287, 115 S.Ct. 1483, 131 L.Ed.2d 385 (1995) (quotations omitted).

The majority in essence concludes that it is not impossible for Wyeth to comply with both federal and state standards because Wyeth never sought FDA approval of a "stronger warning" of the type advocated by plaintiff. According to the majority, because the FDA was not presented with, and therefore did not explicitly reject, such strengthened language, there is no reason to presume that

the FDA would disapprove. Therefore, the majority reasons, there is no actual conflict between state and federal law. See ante ¶ 21-22. It is inaccurate, however, to characterize the requirements imposed by the jury verdict in this case as merely requiring a "stronger warning." Rather, what plaintiff sought was an elimination of a use of Phenergan that had been approved by the FDA. Furthermore, the FDA's rejection of Wyeth's efforts to alter the language of the warning in 2000 supports Wyeth's claim that the FDA had an affirmative preference for the language of the original warning.

A.

The crux of plaintiff's claim was not based on the label warnings per se, but on the approved uses listed there. See, e.g., ante ¶ 3 ("Plaintiff's experts testified that the label should not have allowed IV push as a means of administration...."). A review of plaintiff's complaint and the evidence presented at trial makes clear that the standard plaintiff sought to establish (i.e., the change to the label that would be required in light of the jury's finding of liability) was to remove IV administration-or at least certain types-as an approved use. For example, plaintiff's complaint asserted that the warnings on the label were inadequate and that:

> [t]he Phenergan sold by defendant is ... NOT REASONABLY SAFE FOR INTRAVENOUS ADMINISTRATION because the foreseeable risks of harm posed by intravenous administration of the drug are sufficiently great in relation to its foreseeable theraputic benefits that reasonable health care providers, knowing of such foreseeable

> risks and benefits, WOULD NOT PRESCRIBE THE DRUG INTRAVENOUSLY FOR ANY CLASS OF PATIENTS."

(Emphasis added.) In her appellate brief, plaintiff characterizes the evidence as revealing "that Wyeth was aware of research indicating that DIRECT IV ADMINISTRATION OF PHENERGAN WAS UNSAFE." (Emphasis added.) Plaintiff further refers to expert testimony "that the LABEL SHOULD HAVE RESTRICTED PHENERGAN TO INTRAMUSCULAR INJECTION as this method of administration presents no risk of inadvertent arterial injection; or, alternatively, that if IV administration is used, it must be by injecting the Phenergan into a hanging IV bag, not through a direct IV." (Emphasis added.)

Here, the FDA clearly addressed the risks attending IV administration of the drug. The label approved IV administration generally, and specifically warned of the dangers of direct IV administration, including inadvertent arterial injection possibly resulting in amputation. In light of this, it cannot be argued that the FDA did not (1) assess the risk of IV administration, including direct IV administrationand the associated risk of amputation due to inadvertent arterial injection; (2) conclude that the benefits of allowing IV administration with appropriate warnings outweighed the risk; and (3) reach a decision regarding precisely what warning language should be used. These assessments are, in fact, the very essence of the FDA's approval and are in furtherance of the federal objective of advancing public health by balancing the risks and benefits of new drugs and facilitating their optimal use. See 21 U.S.C.

¶ 355(d) (listing factors to be considered in approving or refusing new drug application); 21 U.S.C. ¶ 393(b)(1), (b)(2)(B) (FDA is charged with promoting public health by acting promptly on new drug applications and protecting public health by ensuring that new drugs are both safe and effective).

The majority reconciles this manifest conflict by relying on 21 C.F.R. ¶ 314.70(c), which allows a drug manufacturer to alter a label "[t]o add or strengthen a contraindication, warning, precaution, or adverse reaction" or "add or strengthen an instruction about dosage and administration" prior to FDA approval.[7] On this basis, the majority concludes that Wyeth "was free under ¶ 314.70(c) to strengthen the warning without prior FDA approval." Ante ¶ 22. But, it is an overstatement to claim that manufacturers are "free" to change drug labels under ¶ 314.70(c). To the contrary, a manufacturer may change a label only to add or strengthen a warning, not to eliminate an approved use, as plaintiff would require here. In other words, what plaintiff advocates is not a stronger warning but language that would directly contradict language approved and mandated by the FDA.

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7. This is also the approach employed by the numerous federal district court decisions cited by the majority. Ante ¶ 14, 565 A.2d 1346. Because I disagree with this analysis of the import of ¶ 314.70(c), I do not find these decisions to be persuasive. Instead, I side with the minority view expressed in Needleman, which concludes that ¶ 314.70(c) gives manufacturers very little latitude in unilaterally revising drug labels. *Needleman v. Pfizer, Inc.*, 2004 WL 1773697, at *3 (N.D.Tex.).

Further, the apparent purpose of ¶ 314.70(c) is to allow manufacturers to address newly-discovered risks. See 44 Fed.Reg. 37434, 37447 (June 26, 1979) (allowing supplement to label "whenever possibly harmful adverse effects associated with the use of the drug are discovered"). Even courts that conclude that ¶ 314.70(c) provides manufacturers broad latitude to add warnings to labels acknowledge that such supplements are aimed at previously unknown and unanalyzed risks. See *McNellis v. Pfizer, Inc.*, 2005 WL 3752269, at *6 (D.N.J.) (concluding that ¶ 314.70(c) "was promulgated precisely to allow drug manufacturers to quickly strengthen label warnings when evidence of new side effects [is] discovered") (citing 30 Fed.Reg. 993 (Jan. 20, 1965)); *Kurer v. Parke, Davis & Co.*, 2004 WI App 74, 18, 272 Wis.2d 390, 679 N.W.2d 867 (noting that, under ¶ 314.70(c), "[d]rug manufacturers can strengthen warnings or petition for additional warnings when new risk information arises"). Another section of the regulation makes clear that any changes to a label that exceed the scope of ¶ 314.70(c) are considered "major changes" that require prior approval before the drug may be distributed. ¶ 314.70(b), (b)(2)(v). In short, the regulation does not allow manufacturers to simply reassess and draw different conclusions regarding the same risks and benefits already balanced by the FDA. Here, the FDA had already evaluated the risk of inadvertent arterial injection from direct IV administration of Phenergan, and had mandated warning language for the label to reflect that risk assessment.

In addition, any change accomplished under ¶ 314.70(c) is subject to ultimate FDA review and approval. See ¶ 314.70(c)(7) (providing that FDA may order manufacturer

to cease distribution of drug if it disapproves supplemental application); see also *Needleman v. Pfizer, Inc.*, 2004 WL 1773697, at *3 (N.D.Tex.2004) (noting that changes to label under ¶ 314.70(c) are temporary and "must later be approved by the FDA"). Thus, any additional or different warnings must ultimately be supported by scientific research that meets the FDA's standards. Neither a manufacturer, a state court, nor a state legislature can permanently substitute its judgment of the risk-benefit analysis for that of the FDA.

At its core, plaintiff's argument in this case was not that the warnings on the label were inadequate, but that an approved use (direct IV administration) was in fact unreasonably unsafe. Plaintiff did not seek to "add or strengthen" a warning or a dosage/administration instruction, but rather to eliminate an approved use of the drug. This is a disagreement that cannot be overcome by operation of ¶ 314.70(c). Plaintiff's claim in this case-that a method of administration of the drug should be partially if not entirely eliminated from the labeling-represents a substantive disagreement with FDA policy that goes beyond labeling/warning issues alone. This disagreement creates opposing requirements and a manufacturer could not satisfy both at once.

B.

Wyeth argues that even if ¶ 314.70(c) theoretically allows a manufacturer to make unilateral changes to a drug label, in this case, the FDA actually rejected Wyeth's attempts in 2000 to change the warning regarding intra-arterial injection and amputation. The trial court concluded that the FDA gave only

"passing attention" to the risks of IV administration in 2000. Ante ¶ 4. The majority similarly concludes that the record does not indicate "that the FDA wished to preserve the use of IV push as a method of administering Phenergan." Ante ¶ 23. I cannot agree with this assessment of the record.

Both the original label and Wyeth's proposed alternative were titled "INADVERTENT INTRA-ARTERIAL INJECTION." On the original label, the first two sentences of the warning read:

> Due to the close proximity of arteries and veins in the areas most commonly used for intravenous injection, extreme care should be exercised to avoid perivascular extravasation or inadvertent intra-arterial injection. Reports compatible with inadvertent intra-arterial injection of [Phenergan], usually in conjunction with other drugs intended for intravenous use, suggest that pain, severe chemical irritation, severe spasm of distal vessels, and resultant gangrene requiring amputation are likely under such circumstances.

On the proposed label, the first sentence of the warning read: "There are reports of necrosis leading to gangrene, requiring amputation, following injection of [Phenergan], usually in conjunction with other drugs; the intravenous route was intended in these cases, but arterial or partial arterial placement of the needle is now suspect." While the proposed change to the warning language may not reflect what plaintiff would require in a warning, it cannot be disputed that Wyeth's proposed alternative warning (1) placed greater emphasis on

the risk of necrosis and amputation by referencing it in the first sentence, and (2) gave the FDA the opportunity to consider the specific, alternative warning advanced by Wyeth, as well as the adequacy of the warning in general. Despite this opportunity, the FDA mandated that Wyeth retain the language of the existing warning. The alleged extent of the FDA's consideration of the issue is not relevant, in my view.

In 2000, the FDA confirmed its assessment that health care professionals should be permitted to choose IV administration in its various forms as a means of delivering the drug, where appropriate. Wyeth could not both list all forms of IV administration as an approved use, as required by the FDA, and exclude all or some forms of IV administration as unsafe, as required by the jury's verdict in this case. It would be impossible to comply with both requirements.

II. Obstacle to Federal Purposes and Objectives

I would further conclude that Wyeth has demonstrated actual conflict preemption by showing that plaintiff's state-law failure-to-warn claim poses an obstacle to federal purposes and objectives. The majority does not address this issue, concluding that Wyeth does not have the option of proving this form of actual conflict preemption. The majority reaches this conclusion by relying on the following clause in the 1962 amendments to the FDCA:

> Nothing in the Amendments made by this Act to the Federal Food, Drug, and Cosmetic Act shall be construed as invalidating any provision of State law ... unless there is a direct and positive conflict between such amendments and such provision of state law.

Ante ¶ 26 (quoting Drug Amendments of 1962 (Harris Kefauver Act), Pub.L. No. 87 781, ¶ 202, 76 Stat. 780, 793 (1962)). Citing *Southern Blasting Services, Inc. v. Wilkes County*, 288 F.3d 584, 591 (4th Cir.2002), the majority concludes that the provision "essentially removes from our consideration the question of whether common-law tort claims present an obstacle to the purposes and objectives of Congress," because the 1962 provision "simply restates the principle that state law is superseded in cases of actual conflict with federal law such that compliance with both federal and state regulations is a physical impossibility." Ante ¶ 27 (internal quotations omitted). "In other words," the majority explains, "under any circumstances where it is possible to comply with both state law and the FDCA, the state law in question is consistent with the purposes and objectives of Congress." Id. Thus, the majority eliminates the possibility of proving actual conflict preemption independently through the "obstacle" prong of that standard.

But neither the passage in Southern Blasting on whichthe majority relies nor the United States Supreme Court decision[8] cited as authority in that passage provide an explanation or

8. See *Hillsborough v. Automated Med. Labs.*, 471 U.S. 707, 713, 105 S.Ct. 2371, 85 L.Ed.2d 714 (1985). The cited passage in Hillsborough does not interpret the phrase "direct and positive conflict." It merely cites the different forms of preemption, including the "obstacle" prong. It is worth noting that the federal statute at issue in *Geier v. American Honda Motor Co.*, 529 U.S. 861, 120 S.Ct. 1913, 146 L.Ed.2d 914 (2000) (discussed below), contained an even broader savings clause than the 1962 amendment to the FDCA. The provision in Geier stated simply that the federal safety standard at issue did "not exempt any person from any liability under common law." *Id.* at 868.

even an affirmative statement that the phrase "direct and positive conflict" in the 1962 amendment eliminates the "obstacle" prong of the actual conflict preemption standard. Thus, the majority eliminates one of the two means by which Wyeth may show actual conflict based on a single, unclearly-reasoned Fourth Circuit decision that is itself lacking in case law support. There is no basis for eliminating this prong of the actual conflict standard, and I disagree with the majority's conclusion to the contrary.[9]

Assuming, then, that Wyeth may demonstrate actual conflict preemption by showing that state law is an obstacle to federal regulatory purposes and objectives, I believe the facts here support the conclusion that the state tort-law verdict in this case is preempted. The United States Supreme Court's decision in *Geier v. American Honda Motor Co.*, 529 U.S. 861, 120 S.Ct. 1913, 146 L.Ed.2d 914 (2000), is controlling on the question of when state law poses an obstacle to federal purposes and objectives. In that case, the Department of Transportation had issued a safety standard that required automobile manufacturers "to equip some but not all of their 1987 vehicles with passive restraints." *Id.* at 864-65. Among the optional passive restraints were air bags. Honda was in

9. Nonetheless, the Court concluded that all ordinary preemption principles-including actual conflict preemption and the obstacle prong of the standard-applied. The Court rejected the notion that Congress would so limit the effect of preemption as to allow an actual conflict with a federal objective: "Insofar as petitioners' argument would permit common-law actions that 'actually conflict' with federal regulations, it would take from those who would enforce a federal law the very ability to achieve the law's congressioally mandated objectives that the Constitution, through the operation of ordinary pre-emption principles, seeks to protect." *Id.* at 872.

compliance with this standard. Nonetheless, the plaintiff was seriously injured in a car accident while driving a 1987 Honda that was not equipped with an air bag, but with another form of passive restraint. The plaintiff brought suit, alleging Honda was negligent in failing to install a driver's-side air bag in the car. Honda argued that the federal safety standard preempted the plaintiff's state-law negligence claim. The Supreme Court held that a lawsuit premising negligence on the failure to install an air bag conflicted with the objectives of the federal safety standard and was therefore preempted. *Id.* at 866.

In reaching this conclusion, the Court noted that the plaintiff and the dissenting opinion-like the majority in the instant case-viewed the federal regulation as setting a minimum safety standard that states were free to supplement or strengthen. *Id.* at 874. However, by examining the comments accompanying the regulation, the Court concluded that a safety standard allowing a choice of passive restraint systems while not mandating any particular system was a deliberate decision that reflected a balance of diverse policy concerns. See *id.* at 875 (noting that allowing mix of available safety devices available over time would "lower costs, overcome technical safety problems, encourage technological development, and win widespread consumer acceptance"). "In sum, ... the 1984 version of [the safety standard] embodies the Secretary's judgment that safety would best be promoted if manufacturers installed alternative protection systems in their fleets rather than one particular system in every car." *Id.* at 881 (quotations omitted). Accordingly, the Court concluded that the tort action sought to impose a duty on manufacturers to impose air bags, rather than other types of

passive restraint systems, and that this state-law requirement was an obstacle to the federal objective of allowing a mix of safety devices.

Application of the Supreme Court precedent in Geier dictates the same result in this case. As with the DOT in Geier, the FDA is primarily concerned with public safety. The conclusion of what is best for public safety is arrived at by considering various policy factors that are sometimes in tension with one another. For example, in developing the safety regulation at issue in Geier, the DOT considered not only which passive-restraint systems were safest on an absolute scale, but which were most cost-effective and which would gain consumer acceptance. Similarly, here the FDA balances its assessment of a drug's safety against concerns for the drug's efficacy, taking into account that a safer but less effective drug is not necessarily best for the public health overall. See 21 U.S.C. ¶ 355(d) (FDA must consider safety and efficacy); 21 U.S.C. ¶ 393(b)(1), (b)(2)(B) (FDA's mission is to protect public from unsafe drugs and to promote public health by approving regulated products in timely manner). In the specific context oarnings on drug labels, the FDA considers not only what information to include, but also what to exclude. As the Eighth Circuit has noted in the medical device context, "[t]here are ... a number of sound reasons why the FDA may prefer to limit warnings on product labels." See *Brooks v. Howmedica, Inc.*, 273 F.3d 785, 796 (8th Cir.2001). For example, "warning about dangers with less basis in science or fewer hazards could take attention away from those that present confirmed, higher risks." *Id.*

Appendix A

No drug is without risks. The FDA balances the risks of a drug against its benefits to maximize the availability of beneficial treatments. The FDA's decision in approving a drug, its uses and labeling reflect consideration of these and other policy factors. While a state-court jury presumably shares the FDA's concern that drugs on the market be reasonably safe, the jury does not assess reasonableness in the context of public health and the associated risk-benefit analysis. A jury does not engage in a measured and multi-faceted policy analysis. Rather, a jury views the safety of the drug through the lens of a single patient who has already been catastrophically injured. Such an approach is virtually guaranteed to provide different conclusions in different courts about what is "reasonably safe" than the balancing approach taken by the FDA. In act, different conclusions were reached in this case.

The jury in this case was instructed that "[a] prescription drug is unreasonably dangerous due to inadequate warnings or instructions if reasonable instructions regarding foreseeable risks of harm are not provided to the physician and other medical professionals who are in a position to reduce the risks of harm." Faced with plaintiff's tragic injuries, the jury concluded that allowing *Phenergan* to be delivered through IV administration was "unreasonably dangerous." The jury's verdict conflicts squarely with the FDA's assessment of precisely the same issue: whether *Phenergan* is safe and effective when delivered through IV administration. The claim is preempted.

For the above reasons, I dissent.

Chief Justice

APPENDIX B — DECISION OF THE SUPERIOR COURT OF WASHINGTON COUNTY FILED AUGUST 2, 2004

STATE OF VERMONT
COUNTY OF WASHINGTON, SS.

Washington Superior Court
Docket No.: 670-12-01

DIANE LEVINE,

Plaintiff,

v.

AMERICAN HOME PRODUCTS, INC.
(now WYETH),

Defendant.

DECISION ON MOTION FOR JUDGMENT UNDER V.R.C.P. 50

This is a motion for judgment under Rule 50 following entry of judgment in a product liability case. The motion was timely filed and follows an earlier motion for judgment on the same grounds submitted at the close of the evidence.

Factual Background

This case arises out of an incident on April 7, 2000, when plaintiff received an injection of the drug Phenergan from physician's assistant Jessica Fisch at the Health Center in Plainfield, Vermont. Phenergan is an anti-nausea medication

manufactured and sold by defendant. As a result of the injection, plaintiff developed gangrene in her right hand. She underwent an amputation of her right arm at the elbow. Plaintiff settled a separate claim against the Health Center and her physician prior to suit.

The parties tried this case from March 8–March 11, 2004. The jury verdict was for $7,400,000. The parties stipulated to adjustments for the prior settlement and pre-judgment interest. The Court entered judgment on March 17, 2004, for $6,774,000.

Standard of Review

The standard of review for a Rule 50 motion is whether "during a trial by jury a party has been fully heard on an issue and there is no legally sufficient evidentiary basis for a reasonable jury to find for that party on that issue." V.R.C.P. 50(a). If the basis for the jury's verdict is insufficient, "the court may determine the issue against that party." *Id.* The trial court may grant the motion against a party "with respect to a claim or defense that cannot under the controlling law be maintained or defeated without a favorable finding on that issue." *Id.*; see also *Brueckner v. Norwich University*, 169 Vt. 118, 122 (1999) ("[A] trial court considers the evidence in the light most favorable to the nonmoving party, excluding the effect of any modifying evidence.") (citation omitted).)

Appendix B

I. Federal Preemption by FDA approval of Phenergan labeling

Plaintiff's claim against defendant is based on allegations that defendant failed to warn of the hazards of intravenous injection of Phenergan. At trial plaintiff introduced evidence that Phenergan should be administered by intra-muscular injection or through a free-flowing IV bag. Plaintiff's witnesses testified that injection into the patient's vein through a "butterfly" infusion set was too dangerous and should have been strongly discouraged in the instructions for use – the "package insert" or label which accompanies the product when it is provided to a physician.

Defendant argues that the approval of the Phenergan label by the Food and Drug Administration preempts Vermont product liability law on the issue of labeling and provides a defense as a matter of law to a claim based on failure-to-warn.

Factual Record at Trial

At trial defendant received wide latitude to introduce evidence about its interaction with the FDA concerning the Phenergan label. The factual record relevant to the Rule 50 motion is as follows:

1. The corrosive nature of Phenergan can lead to catastrophic tissue damage if it enters a patient's arterial blood flow. As the arteries become smaller and more diffuse, the tiny vessels can be damaged by exposure to Phenergan. The patient suffers spasm of the arteries, inflammation, loss of blood flow due

to clotting, gangrene, and, in some cases, the loss of a limb or other serious injury. Green. Tr. 212, 216. Once Phenergan enters the arterial flow, there is no reliable way to reverse the harmful effects of the medication on the tiny vessels distal (downstream) from the site of the injection. Green Tr. 213.

2. In this case, plaintiff received an injection of Phenergan through the use of a "butterfly" intravenous infusion set. The butterfly set consists of a needle which is placed in the patient's vein and held in place by two flexible tabs – the "butterfly." The infusion set creates a fixed point of entry into the vein. Medication can then be injected through the infusion set into the patient's vein. Alternatively, the infusion set can be hooked up to a free-flowing IV bag. Medication such as Phenergan can be added to the IV solution and administered through the IV drip. Matthews, Tr. 85–100. Ms. Fisch injected 50 milligrams of Phenergan directly through the butterfly infusion set into plaintiff's arm over the course of several minutes. She did not use a free-flowing IV bag. Matthews, Tr. 89–93.

3. For reasons that remain unclear, the Phenergan entered plaintiff's arterial system, either because the needle in the infusion set entered an artery directly or because the drug leaked out of the vein and entered an artery through a process called extravasation. Green Tr. 211. As a result of the injection, plaintiff suffered catastrophic injury to her right arm.

4. One way to reduce the risk of inadvertent intra-arterial injection is to set up a free-flowing IV bag and introduce the drug into the IV solution. This is an alternative to injection

through the infusion set into a patient's vein. Administration through a free-flowing IV bag reduces the risk of inadvertent arterial injection because the nurse or physician can be more certain that the needle has been placed in a vein. A solution dripping from an IV bag will not flow freely into an artery due to back pressure from the patient. Green Tr. 194–98, 208–14.

5. The FDA has approved the label for Phenergan since at least 1974. Defendant Ex. P.

6. Since at least 1976, both the FDA and defendant have recognized that injection of Phenergan into an artery is dangerous and can result in severe injury. Defendant Ex. R. By 1976, the Phenergan label contained specific warnings about the hazard of intra-arterial injection. Defendant Ex. S.

7. The minutes of an FDA anesthesiology advisory committee meeting on 10/14/76 include discussion of the Phenergan label then in use. The committee considered a variety of concerns including the risk of intra-arterial injection. The committee recommended that an additional warning should be added: "If a Tubex system is used for intravenous injection, the drug should be injected into a satisfactorily functioning intravenous set." Ex. S.

8. In 1979, the FDA required extensive relabeling of pharmaceutical drugs, including Phenergan. The defendant gave some consideration to changing the warnings about intra-arterial injection to recommend use of an intravenous infusion set for administration of the drug. A 1981 proposed package insert contained the following language:

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> When administering any irritant drug intravenously, it is usually preferable to inject it through the tubing of an intravenous infusion set that is known to be functioning satisfactorily.

Ex. T. Defendant submitted the same proposed language to the FDA on 5/3/88 in conjunction with other proposed changes to the Phenergan label. Ex. M. The proposed language was never used.

9. In a letter to defendant dated 2/21/97, an FDA official directed defendant to "retain verbiage in current label" with respect to the risk of inadvertent intra-arterial injection. No warning or instruction concerning the preferred use of an intravenous infusion set appeared in the defendant's label, including the label in use when the dose of Phenergan involved in this case was sold.

10. The letter dated 2/21/97 identifies the "current label" as the version which defendant submitted to the FDA by letter on 8/6/96. The defendant was unable to obtain a copy of the 8/6/96 letter until after the completion of the trial. The Court will accept and consider this post-trial filing as it relates to the issue of preemption. Preemption is an issue for the Court, not the jury. The post-trial filing removes an area of confusion identified by the Court in the summary judgment decision dated 12/23/03.

11. The 8/6/96 letter from defendant to the FDA contains minor revisions of an earlier label submitted in 1992. It confirms that in 1997, the FDA approved various label changes for Phenergan and rejected the language which

defendant proposed in 1981 and 1988 concerning the preferred use of an intravenous infusion set for administering irritant drugs.

12. Plaintiff's expert witness Harold Green, M.D. testified that the warnings and instructions on the Phenergan label at the time of plaintiff's injury were inadequate to make the product safe because the defendant did not warn sufficiently of the risk of intravenous injection. Dr. Green testified that there was little medical justification for administration of Phenergan intravenously because of the availability of an intramuscular injection. If a physician chose intravenous administration of the drug, the use of a free-flowing IV bag would be safer than injection through a butterfly infusion set. Green Tr. 232–33.

13. Defendant's expert witness David Greenblatt, M.D. disagreed with Dr. Green. He testified that the clinician should remain free to decide whether to administer Phenergan intravenously instead of by intramuscular injection. Greenblatt Tr. 26–27. Dr. Greenblatt agreed with Dr. Green that it was safer to administer Phenergan through a free-flowing IV than by direct intravenous injection. Greenblatt, Tr. 49. Dr. Greenblatt testified that the butterfly infusion set could be considered to be a form of free-flowing IV administration. Greenblatt, Tr. 49.

Analysis

In any preemption case, the only issue is whether Congress intended to exercise the authority provided by the Supremacy Clause to serve as the exclusive source of law. U.S. Const.

art. VI, cl. 2; see also M. Carrier, *Federal Preemption of Common Law Tort Awards by the Federal Food, Drug, and Cosmetic Act*, 51 Food & Drug L.J. 509, 510–11 (1996). In a system in which federal and state law frequently overlap and occupy the same ground, the Supreme Court has consistently required restraint from the lower courts in striking down state remedies. See, e.g., *Silkwood v. Kerr-McGee Corp.*, 464 U.S. 238, 249–57 (1984) (allowing state court imposed punitive damages against nuclear rod manufacturer despite extensive federal regulation over atomic energy). The issue is defined by and limited to the search for Congressional intent expressed in specific legislation. Preemption analysis does not depend upon whether a judge believes that federal regulation of conduct is preferable for reasons of consistency or greater technical expertise.

The starting point for any analysis is the basic assumption that Congress did not intend to displace state law in passing legislation. *Maryland v. Louisiana*, 451 U.S. 725, 746 (1981). "Thus, while state action is preempted if it specifically frustrates the objectives, narrowly and concretely defined, that underlie federal enactments, no such conclusion follows where the most that can be said is that the direction in which state law pushes someone's actions is in general tension with broad or abstract goals that may be attributed to various federal laws or programs." L. Tribe. American Constitutional Law 1187 (3d ed. 2000). The Supreme Court has stated that there is a strong presumption that "the historic police powers of the States [are] not to be superseded by Federal Act unless that [is] the clear and manifest purpose of Congress." *Rice v. Santa Fe Elevator Corp.*, 331 U.S. 218 (1947); but cf. *Hines v. Davidowitz*, 312 U.S. 52 (1941) (finding federal supremacy

in the field of foreign affairs preempted a Pennsylvania statute requiring foreign aliens to register). In areas of health and safety, the U.S. Supreme Court has long recognized the primary interest of the states in the protection of their citizens. *Florida Lime & Avocado Growers v. Paul*, 373 U.S. 132, 144 (1963).

Congress has enacted preemption legislation in other related fields such as medical devices, 21 U.S.C. § 360k, and cigarette labeling, 15 U.S.C. § 1334, but it has not passed any legislation creating an area of *express* preemption for pharmaceutical labeling. See *Hurley v. Lederle Labs.*, 863 F.2d 1173, 1176 (5th Cir. 1988) (collecting decisions finding no express preemption for pharmaceutical labeling). When Congress has not enacted an express preemption provision, the courts must consider whether its intent to preempt state law can be fairly *implied*. The traditional bases for *implied* preemption are: (1) a comprehensive regulatory scheme which occupies the field so completely as to leave no room for state action (field preemption); (2) state law which obstructs the purpose of federal legislation (obstruction conflict preemption); or (3) a direct conflict between state and federal law (direct conflict preemption). *Hillsborough County, Fla. v. Automated Medical Laboratories*, 471 U.S. 707, 713 (1985). Under this standard, defendants argue that the breadth of FDA activity and the potential for interference with its regulatory decisions creates a basis for *implied* presumption. The breadth of activity is a basis for a claim of *field* preemption. The potential for interference is a basis for claims of *conflict* preemption. The Court will address each separately.

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Field Preemption

Since 1906, the Food and Drug Administration – then functioning as the Bureau of Chemistry – has reviewed and approved pharmaceutical labels under Congressional authority. 1906 Food and Drugs Act, ch. 3915, 34 Stat. 768 (repealed by the Federal Food, Drug, and Cosmetic Act of 1938, codified at 21 U.S.C. §§ 301 *et seq.* (2000)). The regulation of labeling is mandatory. Even minor changes require FDA approval. At the same time that the FDA has regulated pharmaceutical labels, plaintiffs in every state have filed tort claims against drug manufacturers on common law causes of action – principally strict liability for failure-to-warn. See, e.g., *McCallister v. Purdue Pharma L.P.*, 164 F.Supp. 2d 783, 787 (S.D. W. Va. 2001).

FDA regulation and state law tort remedies have co-existed for decades – generally to the consternation of the manufacturers. Despite countless "failure-to-warn" cases, filed over several decades, defendants have not identified an authoritative line of cases in which FDA regulation of pharmaceutical labels has been held to preempt the state law remedy of strict liability.

The evidence in this case demonstrates that FDA regulation of labeling is mandatory and comprehensive. It has long operated in conjunction with state law tort claims. Both the Restatement (Second) and Restatement (Third) of Torts: Product Liability permit manufacturers to offer evidence of compliance with FDA requirements as evidence of lack of defect. Restatement (Third) of Torts: Product Liability § 4 (1998); Restatement, Second, of Torts § 288c (1965).

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Compliance with the FDA regulations alone has never been held to be a bar as a matter of law to state law claims that a manufacturer failed to provide an adequate warning. Compare *Caraker v. Sandoz Pharmaceuticals Corp.* 172 F. Supp. 2d 1018, 1030–39 (S.D. Ill. 2001), with *McCallister*, 164 F. Supp. 2d at 792–93 (noting some preemption implications of the Controlled Substances Act).

The absence of an express preemption provision in the enabling legislation for FDA regulation is strong evidence that Congress has chosen not to preempt state law remedies in the area of pharmaceutical labeling. Cf. *Jones v. Rath Packing Co.*, 430 U.S. 519, 537 (1977) ("If Congress had intended to overrule this longstanding . . . practice, founded on a legislative statement of necessity, we would expect it to have done so clearly."); but cf. *Hurley*, 863 F.2d at 1179 (suggesting that the pervasiveness of FDA label regulations would preempt state action involving the adequacy of vaccines warnings). The *express* preemption provisions for medical devices, 21 U.S.C. § 360k, cigarettes 15 U.S.C. § 1334, and pesticides 7 U.S.C. § 136v(b), (FIFRA), demonstrate that Congress knows how to enact preemptive legislation when necessary. Se *Cipollone v. Liggett Group, Inc.*, 505 U.S. 504, 518–20 (1992) (interpreting express statutory preemption). These are obviously different than the implied preemption cases because Congress has spoken aloud and expressly on the issue.

The great majority of courts considering the issue have held that state law claims are not preempted by the dominant presence of the FDA in the field. See *Caraker*, 172 F.Supp. 2d at 1038–39; *Foyle v. Lederle Labs.*, 674 F.Supp 530, 533

(E.D.N.C. 1987); *Carlin v. Superior Court*, 920 P.2d 1347, 1352–53 (Cal. 1996); *Washington State Physicians Ins. Exch. & Assoc. v. Fisons Corp.*, 858 P.2d 1054, 1069 (Wash. 1993); *Feldman v. Lederle Labs*, 625 A.3d 1066, 1070 (N.J. 1993); *Plenger v. Alza Corp.*, 13 Cal.Rptr. 2d 811, 819 n.7 (1992); but see *Ehlis v. Shire Richwood, Inc.*, 233 F. Supp.2d 1189, 1197–98 (D.N.D. 2002) (dicta suggesting preemption through the medical device amendment might apply). The sheer number of these decisions demonstrates that this is not a new issue on which Congress has not had an opportunity to act.

The requirement that pharmaceutical labels be approved by the FDA is insufficient to overcome the presumption against implied preemption. This Court finds no basis for denying plaintiff her remedies under state law on the basis of field preemption.

Conflict Preemption – Obstruction

Whether state law damage claims actually impede the FDA in the pursuit of its mission is hard to see from the limited context of a single personal injury trial. Successive political administrations have differed on this issue. In 1998, the FDA posted its final version of new rules governing the labeling of prescription drugs and clarified that the rules did not in any way preempt tort liability or a manufacturer's duty to warn. *Prescription Drug Product Labeling; Medication Guide Requirements*, 63 Fed. Reg. 66378, 66383–84 (Dec. 1, 1998). More recently, the FDA has had occasion to take the opposite position. Brief of Amicus Curiae United States, *Motus v. Pfizer, Inc.*, 358 F.3d 659 (9th Cir. 2004) (Nos. 02-55372, 02-55498) (urging the court to affirm summary

judgment because FDA regulations preempted plaintiff's duty to warn claim).

The perception of the administrative agency that its work is obstructed is not the standard at issue. Cf. *INS v. Cardoza-Fonseca*, 480 U.S. 421 (1987); *Chevron U.S.A., Inc. v. Nat. Resources Def. Council*, 467 U.S. 837 (1984) (rejecting outright deference to an agency's statutory interpretation in favor of an analysis of congressional intent and traditional statutory construction). It is only the intention of Congress that matters. See *Jones*, 430 U.S. at 525. Many agencies may believe that they possess comprehensive expertise in their field and that any requirement of law arising from another source interferes with their work.

Some tension between the FDA and common law tort remedies is natural, inevitable, and probably healthy. The two sources of law function to meet very different concerns. The tort process does not propose to provide policy and rules applicable to the entire pharmaceutical industry. Instead, it is concerned with compensating individuals for wrongs and providing pressure to curb negligent behavior and the sale of defective products. The FDA regulatory process does not propose to provide compensation in individual cases. Instead, it seeks to provide rules concerning testing, developing and labeling of pharmaceutical drugs which apply to all companies.

The record in this case does not indicate that the work of the FDA has been obstructed by the potential exposure of the manufacturer to state law tort liability. The evidence in this case is that a concern about inadvertent intra-arterial injection

surfaced by 1979 and was the subject of a relatively mild warning proposed by the defendant in 1981 and again in 1988. The FDA rejected the proposed labeling change 9 years later in 1997 in a brief comment. There is no evidence in this record that either the FDA or the manufacturer gave more than passing attention to the issue of whether to use an IV infusion to administer the drug. The proposed labeling change did not address the use of a free-flowing IV bag. Viewing the matter in hindsight through the lens of a single catastrophic case, this Court heard little evidence that the FDA reviewed the issue of the intravenous administration of Phenergan with scientific rigor or any sense of urgency.

This record is very different from the type of intensive regulation described by the Justice Department in their brief submitted in a May 2004 medical device case (*Horn v. Thoratec*). Ex. A to Wyeth's Memo dated 4/16/04. In that brief, the government described a comprehensive pre-market approval process for medical devices requiring an average of 1,200 hours of review time by the agency, thousands of pages of documentation, and substantial give-and-take between the agency and the manufacturer. Brief at p. 8, 21. According to the Justice Department, revision of an existing PMA follows an equally stringent and rigorous process. That is a very different process from the leisurely course of review for the Phenergan label changes conducted over some sixteen years. The regulatory process in this case was marked by long periods of dormancy and a conclusory decision in 1997 to require no change to the existing label. The recommendation of administration through a free-flowing IV bag never appears in the regulatory record. In short, a tort case is unlikely to obstruct the regulatory process when the

record shows that the FDA has paid very little attention to the issues raised by the parties at trial.

The principal basis for obstruction advanced by proponents of implied preemption in the pharmaceutical field is concern that excessive or unwarranted warnings will reduce the use of a safe and valuable medication. See Justice Department Brief in *Horn v. Thoratec* at 25–26; R. Pear, *In a Shift, Bush Moves to Block Medical Suits*, N.Y. Times, July 25, 2004, available at *http://www.nytimes.com/2004/07/25/politics/25DRUG.html*. The problem of "defensive warning" is not strong in this case. Any warning or instruction about the greater safety of a free-flowing IV bag relates only to the method of administration, not to the decision to use Phenergan. This case is different from cases involving proposed warnings of remote side effects which might dissuade physicians from using the drug to the detriment of the patient population.

There is no basis in this case to conclude that the work of the FDA was obstructed in any way by the indirect pressure of state law tort liability.

Conflict Preemption – Direct Conflict

The FDA regulations and a state law failure-to-warn case do not conflict directly. Compliance with the FDA labeling regulations is not a complete defense, but the manufacturer is entitled to raise it as a defense as defendant has done in this case. Restatement (Third) of Torts: Product Liability § 4. The record in this case is mixed concerning the ability of the defendant to provide a sharper warning about the risks

of intravenous injection. While the defendant insisted that severe sanctions, including criminal prosecution, would follow any change to the label as approved by the FDA in 1981 and 1997, the FDA regulations permit strengthened warnings without approval on an interim basis. 21 C.F.R. 314.70; see also *Kurer v. Parke, Davis & Co.*, 679 N.W. 2d 867, 872–74 (Wis. App. 2004).

More fundamentally, compliance with federal regulation does not provide a complete defense against tort liability. In a three-member partially dissenting opinion in *Cipollone v. Liggett Group*, 505 U.S. 504 (1992), Justice Blackman wrote:

> The effect of tort law on a manufacturer's behavior is necessarily indirect. Although an award of damages by its very nature attaches additional consequences to the manufacturer's continued unlawful conduct, no particular course of action (*e.g.*, the adoption of a new warning label) is required. A manufacturer found liable on, for example, a failure-to-warn claim may respond in a number of ways. It may decide to accept damages awards as a cost of doing business and not alter its behavior in any way. Or, by contrast, it may choose to avoid future awards by dispensing warnings through a variety of alternative mechanisms, such as package inserts, public service advertisements, or general educational programs. The level of choice that a defendant retains in shaping its own behavior distinguishes the indirect regulatory effect of the common law from positive enactments such as

> statutes and administrative regulations. Moreover, tort law has an entirely separate function – compensating victims – that sets it apart from direct forms of regulation.

Id., 505 U.S. 536–37 (citations omitted). There is no direct conflict between the FDA regulatory process and the common law remedy. The record in this case was that there have been at least 20 reports of amputations similar to plaintiff's injury since the 1960s. Green, Tr. 216. The defendant has remained in compliance with the FDA regulations by retaining the same warning about the risks of intra-arterial injection for several decades. This warning may be insufficient – certainly this jury found it to be so – and the result is that on some occasions the defendant may pay compensation. This tension does not amount to a direct conflict with the FDA labeling requirements. "The reason why many courts find no preemption is that the FDA's drug labeling decisions impose only 'minimum' standards that are open to supplementation by state law through a jury's verdict enforcing a manufacturer's common law duty to warn." *Caraker*, 172 F. Supp. 2d at 1033. The record in this case of a slow and imperfect regulatory process illustrates why courts have consistently held that FDA regulation provides a minimum standard of safety.

This Court finds no basis for federal preemption on grounds of direct conflict.

Appendix B

II. Causation

Defendant seeks to attribute sole causation as a matter of law to the actions of Jessica Fisch, P.A. who continued to inject the Phenergan despite a statement from the plaintiff that the injection hurt. This argument raises factual issues which were argued to the jury and resolved in plaintiff's favor at trial.

First, there is a factual dispute about whether it was too late for Ms. Fisch to stop the injection if the burning sensation experienced by the plaintiff was the Phenergan entering an artery. Second, the defendant requested and received a detailed instruction on efficient intervening cause, which addressed the same issues raised in this motion. Third, and most importantly, warnings are almost never the *sole* cause of an injury. Injury occurs only after the warning combines with human conduct to produce at least two concurrent causes of the event. *Gilman v. Towmotor Corp.*, 160 Vt. 116, 119–20 (1992); see also Restatement (Third) of Torts: Product Liability § 2 cmt. m (foreseeability); *id.* at § 16 (increased harm due to product defect). The warning is read – or not – by some human actor who follows it – or not. If subsequent human action were enough to break the chain of causation, there would be no cause of action for failure-to-warn. Restatement (Third) of Torts: Products Liability § 17.

The plaintiff's claim is not that Ms. Fisch was without blame or fault. Rather, as this Court understands it from trial, the claim is that if Ms. Fisch and her supervising physician had been told of the risk of limb death and amputation, she would have administered Phenergan by a safer method than the

butterfly infusion set. In rejecting the defense of efficient intervening cause, the jury decided that any conduct by Ms. Fisch did not break the chain of causation. There is sufficient evidence from Ms. Fisch, Dr. Matthews, and Dr. Green to support the jury's conclusion. This evidence is principally the testimony from Dr. Matthews that he would never have permitted administration of Phenergan through direct injection at his clinic if he had known of the risks to the patient and the testimony from Dr. Green that use of a free-flowing IV bag or intramuscular injection are safer methods of administering the drug.

Plaintiff argued at trial that a safer method of administration would have greatly reduced the risk of injury from inadvertent arterial injection. The defendant argued that injection through the butterfly-infusion set remains an appropriate method of administration. The jury rejected this defense and accepted the plaintiff's version of the facts. The Court will not overturn the verdict on a factual issue when there is evidence to support the jury's conclusion.

III. Damages

Defendant seeks a new trial for damages on the grounds that the Court did not grant a present value instruction for general damages (non-economic damages), which resulted in an oversized general damages award ($5,000,000). No challenge is raised to the award of special damages (medical and rehabilitative expenses and lost income) in the amount of $2.4 million.

Appendix B

A. Present Value Instruction

In this case, the Court rejected defendant's request for an instruction that any award of future general damages should be reduced to present value. There were several reasons for this.

First, the defendant put on no proof or argument concerning how to reduce future pain and suffering to present value. Nor, of course, did plaintiff. Future *economic* damages were always reduced to present value by plaintiff's economist and were essentially conceded without challenge by defendant. See, e.g., *Girroir v. Carpenter*, 136 Vt. 290, 292 (1978); *Wolfe v. Mendel*, 84 N.W.2d 109, 111, 115 (Neb. 1957) ("Where an instruction does not prohibit or negative the computation of damages upon the basis of their present worth, it will not be assumed that the jury did not understand that it was to estimate the present value of future earnings lost."). The defense never proposed a method by which the jury could discount for prevailing interest rates while accounting for the effects of expected inflation. Even the 12% discount rate proposed in the post-trial briefs was not suggested.

The briefing on this motion illustrates the practical difficulties of instructing the jury in a meaningful fashion that they should reduce the award of future pain and suffering to present value. The lawyers have presented wildly different proposals and methodologies. The defendant proposes a simple discount rate based on 12% or 2%. It offered no economic opinion at trial.

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On the evidentiary record alone, including closing arguments, there was an inadequate basis for a present value instruction on future pain and suffering.

Second, the majority view – starting with the Restatement (Second) of Torts § 913A cmt. a – is that the calculation of future general damages is too subjective to be subjected to economic analysis by a lay jury. *Flanigan v. Burlington N., Inc.*, 632 F.2d 880, 886 (8th Cir. 1980); *O'Byrne v. St. Louis Southwestern Ry. Co.*, 632 F.2d 1285, 1286 (5th Cir. 1980); *Taylor v. Denver & Rio Grande W. R.R.*, 438 F.2d 351, 353 (10th Cir. 1971) ("[T]he courts [have] held that the better reasoned authority supports the rule that future pain and suffering should not be reduced to current worth."); *United States v. Harue Hayashi*, 282 F.2d 599, 605–06 (9th Cir. 1960); *Texas & Pacific Railway Co. v. Buckles*, 232 F.2d 257, 264 (5th Cir. 1956); *Chicago & N.W. Ry. Co. v. Candler*, 283 F. 881, 885 (8th Cir. 1922) ("The arbitrariness and artificiality of such a method is so apparent that to require a jury to apply it would, we think, be an absurdity."); *Purdy v. Belcher Refining Co.*, 781 F.Supp. 1559, 1563 (S.D. Ala. 1992); *Hanson v. Reiss Steamship Company*, 184 F.Supp. 545, 552–53 (D.Del. 1960) (holding that allowances for future pain and suffering are not subject to reduction to present worth); *Sleeman v. Chesapeake & O. Ry. Co.*, 305 F.Supp. 33, 36 n.1 (W.D. Mich. Sep 09, 1969) vacated, 424 F.2d 547 (6th Cir. 1970); *Schirra v. Delaware, L. & W.R. Co.*, 103 F.Supp. 812, 824 (M.D.Pa. 1952); *Beaulieu v. Elliott*, 434 P.2d 665, 671–72, 676 (Alaska 1967); *Braddock v. Seaboard Air Line R.R.*, 80 So.2d 662, 666–68 (Fla. 1955); *Delva v. Value Rent-A-Car*, 693 So.2d 574, 578 (Fla.App. 1997); *Bagley v. Akins*, 138 S.E.2d 430, 431 (Ga.App. 1964); *Brant v. Bockholt*, 532

N.W.2d 801, 803–04 (Iowa 1995) (collecting cases); *Louisville & N.R. Co. v. Gayle*, 263 S.W. 763 (Ky. 1924); *Busch v. Busch Const., Inc.*, 262 N.W.2d 377, 397 (Minn. 1977); *Barlage v. The Place, Inc.*, 277 N.W.2d 193, 195 (Minn.Sup.Ct. 1979); *Dickerson v. St. Louis S.W. Ry.*, 697 S.W.2d 210, 212 (Mo.App.1985); *Ball v. Burlington N. R.R.*, 672 S.W.2d 358, 361 (Mo.App. 1984); *Porter v. Funkhouser*, 382 P.2d 216, 218–19 (Nev. 1963); *Friedman v. C&S Car Serv.*, 527 A.2d 871, 873–75 (N.J. 1987); *Bready v. Tipton*, 407 P.2d 194, 206 (Okla. 1965); *Yost v. West Penn. Ry. Co.*, 9 A.2d 368, 369–70 (Pa. 1939); *Missouri Pac. R.R. v. Handley*, 341 S.W.2d 203, 205 (Tex.Civ.App. 1960); *Borzea v. Anselmi*, 258 P.2d 796, 804 (Wyo. 1952); 22 Am. Jur.2d *Damages* § 999 ("[T]he generally accepted rule is that the award [for pain and suffering] is not to be thus reduced [to present worth]."); see also *Oliveri v. Delta S.S. Lines, Inc.*, 849 F.2d 742, 750–52 (2d Cir. 1988) (noting that the majority of state jurisdictions do not reduce future pain and suffering awards and criticizing the rule requiring reduction to present value); *Hogan v. Santa Fe Trail Transportation Co.*, 85 P.2d 28, 34–38 (Kan. 1938) (Wedell, J., dissenting) (collecting early cases); *McKenna v. State*, 492 N.Y.S.2d 805, 807 (1985).

Third, it would involve the Court and the jury in something of a charade to pretend that without expert guidance, the jurors are capable of running accurate present value calculations on general damage awards proposed during deliberations. Judges and lawyers are universally incapable of performing the discount calculations with or without a calculator and the tables of historic interest rates and inflationary factors. It is invariably the topic of expert

testimony by an economist, and then only on the elements of special damage such as lost income and future medical bills. As Professor Dobbs succinctly states the issue:

> The Rule requiring reduction to present value must be qualified in several ways. In the first place, viewed realistically, the plaintiff is often not required to put on proof or explanation how reduction is to take place, and if the jury only gets an instruction to make the reduction without any further explanation, the rule probably does not mean very much. Beyond this, there is the agreed limit to the rule that only pecuniary losses are reduced. Thus awards for future pain and suffering, or for the future loss of companionship or guidance, are made without reduction. Presumably this is because it would be futile and even misleading to compute mathematically a reduction on an award that could have no mathematical basis in the first place.

D. Dobbs, *Handbook on the Law of Remedies* § 8.7, at 574 (1st ed. 1973).

For this reason, the Vermont Supreme Court has limited *pre-judgment* interest to special damages. *Gilman*, 160 Vt. at 121; see also *Bull v. Pinkham Eng'g Assoc.*, 170 Vt. 450, 463–64 (2000); *Ulm v. FordMotor Co.*, 170 Vt. 281, 292–94 (2000); *Remes v. Nordic Group, Inc.*, 169 Vt. 37, 40–41 (1999); *Estate of Fleming v. Nicholson*, 168 Vt. 495, 501–03 (1998); *Winey v. William E. Dailey, Inc.*, 161 Vt. 129, 141 (1993); *Turcotte v. Estate of LaRose*, 153 Vt. 196, 198–200 (1989).

It would be uneven at best to eliminate pre-judgment interest on general damages while requiring a reduction for future awards. Cf. Restatement (Second) of Torts § 913A cmt. a (linking present worth valuations with § 912 and its prohibition on prejudgment interest for pain and suffering). The reasoning that it is

The Court will not grant a new trial on the basis of the jury charge on general damages.

B. Reasonableness of the general damage award

Defendant cites several Vermont verdicts ranging from $1 million to $3 million recorded between 1977 and 1999. Defendant argues that at $5 million for general damages, this verdict is too high. Defendant does not take issue with the award of $2.4 for special damages and did not challenge the proof on that issue at trial.

This Court will not remit or set aside the damages verdict because the damage award is reasonably supported by the proof at trial. *Dean v. Arena*, 141 Vt. 647, 650 (1981). Several factors support a high award for pain and suffering.

First, this was an extraordinary case. The defendant describes it as tragic, and the Court saw it the same way at trial. The proof of plaintiff's joy and commitment to music prior to the loss of her arm was very compelling. The immediate effects of the injury were horrific. The changes in plaintiff's life as a result of her injury are wide and deep. This was as bad an injury case as any court is likely to see. What made the case unusual was the way that the injury cut so directly

into the life of a musician. The evidence of plaintiff's suffering and the loss of her ability to play the guitar at a professional level was powerful and undisputed.

Second, the jury verdicts presented by defendant place this verdict at one end of a range of results in serious cases in Vermont. So far as it is possible to tell, this jury verdict is the largest to date in a personal injury case. The verdicts are necessarily incomplete because they do not include settlements. This information is available only at third-hand, but it is generally known within the Vermont legal community; over the course of the last 10 years, a few severe injury cases have settled for amounts in excess of the verdicts listed by defendant. In October 2002, the Lamoille Superior Court entered judgment in a case involving quadriplegia for $48,000,000 following a bench trial. *Perron v. Vt. Utility Serv. Inc.*, No. 154-8-01LeCv (Cashman, J., Oct. 2002). On April 8, 2004, the Addison Superior Court entered judgment for $2,345,764 after a damages hearing in a default case concerning a severe foot injury. *Hadvab v. Manning*, No. 121-6-03 Ancv, 8 Vt.TrialCt.Rep. 274 (Toor, J.) This Court does not rely on these results in any direct evidentiary fashion because the underlying facts are not available for comparison, but they do provide some indication that a $7.4 million dollar verdict is not an isolated event within our legal culture.

The standard for review of a damages award is whether the award is "entirely excessive" or "shocks the conscience." *Turgeon v. Schneider*, 150 Vt. 268, 274 (1988); *Newhall v. Central Vermont Hospital*, 133 Vt. 572, 576–77 (1975). This was a bad damages case. The defendant chose not to challenge the damages at trial. The verdict falls within a range of results

seen in recent years in our state. This Court finds that the verdict is reasonably supported by the evidence and is not excessive for purposes of Rule 50 or Rule 59(a).

CONCLUSION

Defendant's motion for judgment under Rule 50 or, in the alternative, for a new trial on damages is DENIED.

Dated: 7-30-04

s/ Geoffrey W. Crawford
Superior Court Judge

APPENDIX C — DECISION OF THE VERMONT SUPREME COURT FILED DECEMBER 11, 2006, DENYING REARGUMENT

VERMONT SUPREME COURT

DOCKET NO. 2004-384

NOVEMBER TERM, 2006

DIANA LEVINE

v.

WYETH*

APPEALED FROM:
WASHINGTON SUPERIOR

DOCKET NUMBER: 670-12-01 Wncv

ENTRY ORDER

In the above-entitled cause, the Clerk will enter:

Appellant has filed a timely motion for reargument of this Court's October 27, 2006 decision in the above matter. Insofar as appellant has failed to demonstrate that the Court overlooked or misapprehended points of law or fact that would have affected the result, the motion is denied. V.R.A.P. 40.

Appendix C

BY THE COURT:

s/ _____
Paul L. Reiber, Chief Justice

s/ _____
John A. Dooley, Associate Justice

s/ _____
Denise R. Johnson, Associate Justice

s/ _____
Walter M. Morris, Jr., District Judge,
Specially Assigned

s/ _____
Frederic W. Allen, Chief Justice (Ret.),
Specially Assigned

APPENDIX D — CONSTITUTIONAL PROVISION INVOLVED

United States Constitution
Article VI, Clause 2

This Constitution, and the Laws of the United States which shall be made in Pursuance thereof; and all Treaties made, or which shall be made, under the Authority of the United States, shall be the supreme Law of the Land; and the Judges in every State shall be bound thereby, any Thing in the Constitution or Laws of any State to the Contrary notwithstanding.

APPENDIX E — 21 U.S.C. § 393

TITLE 21—FOOD AND DRUGS
CHAPTER 9—FEDERAL FOOD, DRUG, AND COSMETIC ACT
SUBCHAPTER IX—MISCELLANEOUS

Sec. 393. Food and Drug Administration

(a) In general

There is established in the Department of Health and Human Services the Food and Drug Administration (hereinafter in this section referred to as the "Administration").

(b) Mission

The Administration shall—

(1) promote the public health by promptly and efficiently reviewing clinical research and taking appropriate action on the marketing of regulated products in a timely manner;

(2) with respect to such products, protect the public health by ensuring that—

(A) foods are safe, wholesome, sanitary, and properly labeled;

(B) human and veterinary drugs are safe and effective;

(C) there is reasonable assurance of the safety and effectiveness of devices intended for human use;

(D) cosmetics are safe and properly labeled; and

(E) public health and safety are protected from electronic product radiation;

(3) participate through appropriate processes with representatives of other countries to reduce the burden of regulation, harmonize regulatory requirements, and achieve appropriate reciprocal arrangements; and

(4) as determined to be appropriate by the Secretary, carry out paragraphs (1) through (3) in consultation with experts in science, medicine, and public health, and in cooperation with consumers, users, manufacturers, importers, packers, distributors, and retailers of regulated products.

(c) Interagency collaboration

The Secretary shall implement programs and policies that will foster collaboration between the Administration, the National Institutes of Health, and other science-based Federal agencies, to enhance the scientific and technical expertise available to the Secretary in the conduct of the duties of the

Appendix E

Secretary with respect to the development, clinical investigation, evaluation, and postmarket monitoring of emerging medical therapies, including complementary therapies, and advances in nutrition and food science.

(d) Commissioner

(1) Appointment

There shall be in the Administration a Commissioner of Food and Drugs (hereinafter in this section referred to as the "Commissioner") who shall be appointed by the President by and with the advice and consent of the Senate.

(2) General powers

The Secretary, through the Commissioner, shall be responsible for executing this chapter and for—

(A) providing overall direction to the Food and Drug Administration and establishing and implementing general policies respecting the management and operation of programs and activities of the Food and Drug Administration;

(B) coordinating and overseeing the operation of all administrative entities within the Administration;

(C) research relating to foods, drugs, cosmetics, and devices in carrying out this chapter;

(D) conducting educational and public information programs relating to the responsibilities of the Food and Drug Administration; and

(E) performing such other functions as the Secretary may prescribe.

(e) Technical and scientific review groups

The Secretary through the Commissioner of Food and Drugs may, without regard to the provisions of title 5 governing appointments in the competitive service and without regard to the provisions of chapter 51 and subchapter III of chapter 53 of such title relating to classification and General Schedule pay rates, establish such technical and scientific review groups as are needed to carry out the functions of the Administration, including functions under this chapter, and appoint and pay the members of such groups, except that officers and employees of the United States shall not receive additional compensation for service as members of such groups.

(f) Agency plan for statutory compliance

(1) In general

Not later than 1 year after November 21, 1997, the Secretary, after consultation with appropriate scientific and academic experts, health care professionals, representatives of patient and consumer advocacy groups, and the regulated industry, shall develop and publish in the Federal Register a

plan bringing the Secretary into compliance with each of the obligations of the Secretary under this chapter. The Secretary shall review the plan biannually and shall revise the plan as necessary, in consultation with such persons.

(2) Objectives of agency plan

The plan required by paragraph (1) shall establish objectives and mechanisms to achieve such objectives, including objectives related to—

(A) maximizing the availability and clarity of information about the process for review of applications and submissions (including petitions, notifications, and any other similar forms of request) made under this chapter;

(B) maximizing the availability and clarity of information for consumers and patients concerning new products;

(C) implementing inspection and postmarket monitoring provisions of this chapter;

(D) ensuring access to the scientific and technical expertise needed by the Secretary to meet obligations described in paragraph (1);

(E) establishing mechanisms, by July 1, 1999, for meeting the time periods specified in this chapter for the review of all applications and submissions described in subparagraph (A) and submitted after November 21, 1997; and

(F) eliminating backlogs in the review of applications and submissions described in subparagraph (A), by January 1, 2000.

(g) Annual report

The Secretary shall annually prepare and publish in the Federal Register and solicit public comment on a report that—

(1) provides detailed statistical information on the performance of the Secretary under the plan described in subsection (f) of this section;

(2) compares such performance of the Secretary with the objectives of the plan and with the statutory obligations of the Secretary; and

(3) identifies any regulatory policy that has a significant negative impact on compliance with any objective of the plan or any statutory obligation and sets forth any proposed revision to any such regulatory policy.

APPENDIX F — 21 U.S.C. § 355(a)-(e)

TITLE 21—FOOD AND DRUGS CHAPTER 9—
FEDERAL FOOD, DRUG, AND COSMETIC ACT
SUBCHAPTER V—DRUGS AND DEVICES
Part A—Drugs and Devices

Sec. 355. New drugs

(a) Necessity of effective approval of application

No person shall introduce or deliver for introduction into interstate commerce any new drug, unless an approval of an application filed pursuant to subsection (b) or (j) of this section is effective with respect to such drug.

(b) Filing application; contents

(1) Any person may file with the Secretary an application with respect to any drug subject to the provisions of subsection (a) of this section. Such person shall submit to the Secretary as a part of the application (A) full reports of investigations which have been made to show whether or not such drug is safe for use and whether such drug is effective in use; (B) a full list of the articles used as components of such drug; (C) a full statement of the composition of such drug; (D) a full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug; (E) such samples of such drug and of the articles used as components thereof as the Secretary may require; (F) specimens of the labeling proposed to be used for such drug, and (G) any assessments required under section 355c of this title. The applicant shall file with the application the patent number

and the expiration date of any patent which claims the drug for which the applicant submitted the application or which claims a method of using such drug and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug. If an application is filed under this subsection for a drug and a patent which claims such drug or a method of using such drug is issued after the filing date but before approval of the application, the applicant shall amend the application to include the information required by the preceding sentence. Upon approval of the application, the Secretary shall publish information submitted under the two preceding sentences. The Secretary shall, in consultation with the Director of the National Institutes of Health and with representatives of the drug manufacturing industry, review and develop guidance, as appropriate, on the inclusion of women and minorities in clinical trials required by clause (A).

(2) An application submitted under paragraph (1) for a drug for which the investigations described in clause (A) of such paragraph and relied upon by the applicant for approval of the application were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted shall also include—

> (A) a certification, in the opinion of the applicant and to the best of his knowledge, with respect to each patent which claims the drug for which such investigations were conducted or which claims a use for such drug for which the applicant is

seeking approval under this subsection and for which information is required to be filed under paragraph (1) or subsection (c) of this section—

(i) that such patent information has not been filed,

(ii) that such patent has expired,

(iii) of the date on which such patent will expire, or

(iv) that such patent is invalid or will not be infringed by the manufacture, use, or sale of the new drug for which the application is submitted; and

(B) if with respect to the drug for which investigations described in paragraph (1)(A) were conducted information was filed under paragraph (1) or subsection (c) of this section for a method of use patent which does not claim a use for which the applicant is seeking approval under this subsection, a statement that the method of use patent does not claim such a use.

(3) Notice of opinion that patent is invalid or will not be infringed—

Appendix F

(A) Agreement to give notice.—An applicant that makes a certification described in paragraph (2)(A)(iv) shall include in the application a statement that the applicant will give notice as required by this paragraph.

(B) Timing of notice.—An applicant that makes a certification described in paragraph (2)(A)(iv) shall give notice as required under this paragraph—

> (i) if the certification is in the application, not later than 20 days after the date of the postmark on the notice with which the Secretary informs the applicant that the application has been filed; or
>
> (ii) if the certification is in an amendment or supplement to the application, at the time at which the applicant submits the amendment or supplement, regardless of whether the applicant has already given notice with respect to another such certification contained in the application or in an amendment or supplement to the application.

(C) Recipients of notice.—An applicant required under this paragraph to give notice shall give notice to—

(i) each owner of the patent that is the subject of the certification (or a representative of the owner designated to receive such a notice); and

(ii) the holder of the approved application under this subsection for the drug that is claimed by the patent or a use of which is claimed by the patent (or a representative of the holder designated to receive such a notice).

(D) Contents of notice—A notice required under this paragraph shall—

(i) state that an application that contains data from bioavailability or bioequivalence studies has been submitted under this subsection for the drug with respect to which the certification is made to obtain approval to engage in the commercial manufacture, use, or sale of the drug before the expiration of the patent referred to in the certification; and

(ii) include a detailed statement of the factual and legal basis of the opinion of the applicant that the patent is invalid or will not be infringed.

Appendix F

(4)(A) An applicant may not amend or supplement an application referred to in paragraph (2) to seek approval of a drug that is a different drug than the drug identified in the application as submitted to the Secretary.

(B) With respect to the drug for which such an application is submitted, nothing in this subsection or subsection (c)(3) of this section prohibits an applicant from amending or supplementing the application to seek approval of a different strength.

(5)(A) The Secretary shall issue guidance for the individuals who review applications submitted under paragraph (1) or under section 262 of title 42, which shall relate to promptness in conducting the review, technical excellence, lack of bias and conflict of interest, and knowledge of regulatory and scientific standards, and which shall apply equally to all individuals who review such applications.

(B) The Secretary shall meet with a sponsor of an investigation or an applicant for approval for a drug under this subsection or section 262 of title 42 if the sponsor or applicant makes a reasonable written request for a meeting for the purpose of reaching agreement on the design and size of clinical trials intended to form the primary basis of an effectiveness claim. The sponsor or applicant shall provide information necessary for discussion and agreement on the design and size of the clinical trials. Minutes of any such meeting shall

be prepared by the Secretary and made available to the sponsor or applicant upon request.

(C) Any agreement regarding the parameters of the design and size of clinical trials of a new drug under this paragraph that is reached between the Secretary and a sponsor or applicant shall be reduced to writing and made part of the administrative record by the Secretary. Such agreement shall not be changed after the testing begins, except—

> (i) with the written agreement of the sponsor or applicant; or
>
> (ii) pursuant to a decision, made in accordance with subparagraph (D) by the director of the reviewing division, that a substantial scientific issue essential to determining the safety or effectiveness of the drug has been identified after the testing has begun.

(D) A decision under subparagraph (C)(ii) by the director shall be in writing and the Secretary shall provide to the sponsor or applicant an opportunity for a meeting at which the director and the sponsor or applicant will be present and at which the director will document the scientific issue involved.

(E) The written decisions of the reviewing division shall be binding upon, and may not directly or indirectly be changed by, the field or compliance division personnel unless such field or compliance division personnel demonstrate to the reviewing division why such decision should be modified.

(F) No action by the reviewing division may be delayed because of the unavailability of information from or action by field personnel unless the reviewing division determines that a delay is necessary to assure the marketing of a safe and effective drug.

(G) For purposes of this paragraph, the reviewing division is the division responsible for the review of an application for approval of a drug under this subsection or section 262 of title 42 (including all scientific and medical matters, chemistry, manufacturing, and controls).

(c) Period for approval of application; period for, notice, and expedition of hearing; period for issuance of order

(1) Within one hundred and eighty days after the filing of an application under subsection (b) of this section, or such additional period as may be agreed upon by the Secretary and the applicant, the Secretary shall either—

(A) approve the application if he then finds that none of the grounds for denying approval

specified in subsection (d) of this section applies, or

(B) give the applicant notice of an opportunity for a hearing before the Secretary under subsection (d) of this section on the question whether such application is approvable. If the applicant elects to accept the opportunity for hearing by written request within thirty days after such notice, such hearing shall commence not more than ninety days after the expiration of such thirty days unless the Secretary and the applicant otherwise agree. Any such hearing shall thereafter be conducted on an expedited basis and the Secretary's order thereon shall be issued within ninety days after the date fixed by the Secretary for filing final briefs.

(2) If the patent information described in subsection (b) of this section could not be filed with the submission of an application under subsection (b) of this section because the application was filed before the patent information was required under subsection (b) of this section or a patent was issued after the application was approved under such subsection, the holder of an approved application shall file with the Secretary the patent number and the expiration date of any patent which claims the drug for which the application was submitted or which claims a method of using such drug and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug. If the holder of an approved application could not file patent information under subsection (b) of this section because it

was not required at the time the application was approved, the holder shall file such information under this subsection not later than thirty days after September 24, 1984, and if the holder of an approved application could not file patent information under subsection (b) of this section because no patent had been issued when an application was filed or approved, the holder shall file such information under this subsection not later than thirty days after the date the patent involved is issued. Upon the submission of patent information under this subsection, the Secretary shall publish it.

(3) The approval of an application filed under subsection (b) of this section which contains a certification required by paragraph (2) of such subsection shall be made effective on the last applicable date determined by applying the following to each certification made under subsection (b)(2)(A) of this section:

> (A) If the applicant only made a certification described in clause (i) or (ii) of subsection (b)(2)(A) of this section or in both such clauses, the approval may be made effective immediately.
>
> (B) If the applicant made a certification described in clause (iii) of subsection (b)(2)(A) of this section, the approval may be made effective on the date certified under clause (iii).
>
> (C) If the applicant made a certification described in clause (iv) of subsection (b)(2)(A) of this section, the approval shall be made effective

immediately unless, before the expiration of 45 days after the date on which the notice described in subsection (b)(3) of this section is received, an action is brought for infringement of the patent that is the subject of the certification and for which information was submitted to the Secretary under paragraph (2) or subsection (b)(1) of this section before the date on which the application (excluding an amendment or supplement to the application) was submitted. If such an action is brought before the expiration of such days, the approval may be made effective upon the expiration of the thirty-month period beginning on the date of the receipt of the notice provided under subsection (b)(3) of this section or such shorter or longer period as the court may order because either party to the action failed to reasonably cooperate in expediting the action, except that—

> (i) if before the expiration of such period the district court decides that the patent is invalid or not infringed (including any substantive determination that there is no cause of action for patent infringement or invalidity), the approval shall be made effective on—
>
> > (I) the date on which the court enters judgment reflecting the decision; or

(II) the date of a settlement order or consent decree signed and entered by the court stating that the patent that is the subject of the certification is invalid or not infringed;

(ii) if before the expiration of such period the district court decides that the patent has been infringed—

(I) if the judgment of the district court is appealed, the approval shall be made effective on—

(aa) the date on which the court of appeals decides that the patent is invalid or not infringed (including any substantive determination that there is no cause of action for patent infringement or invalidity); or

(bb) the date of a settlement order or consent decree signed and entered by the court of appeals stating that the patent that is the subject of the certification is invalid or not infringed; or

(II) if the judgment of the district court is not appealed or is affirmed, the approval shall be made effective on the date specified by the district court in a court order under section 271(e)(4)(A) of title 35;

(iii) if before the expiration of such period the court grants a preliminary injunction prohibiting the applicant from engaging in the commercial manufacture or sale of the drug until the court decides the issues of patent validity and infringement and if the court decides that such patent is invalid or not infringed, the approval shall be made effective as provided in clause (i); or

(iv) if before the expiration of such period the court grants a preliminary injunction prohibiting the applicant from engaging in the commercial manufacture or sale of the drug until the court decides the issues of patent validity and infringement and if the court decides that such patent has been infringed, the approval shall be made effective as provided in clause (ii). In such an action, each of the parties shall reasonably cooperate in expediting the action.

Appendix F

(D) Civil action to obtain patent certainty.—

(i) Declaratory judgment absent infringement action.—

(I) In general.—No action may be brought under section 2201 of title 28 by an applicant referred to in subsection (b)(2) of this section for a declaratory judgment with respect to a patent which is the subject of the certification referred to in subparagraph (C) unless—

(aa) the 45-day period referred to in such subparagraph has expired;

(bb) neither the owner of such patent nor the holder of the approved application under subsection (b) of this section for the drug that is claimed by the patent or a use of which is claimed by the patent brought a civil action against the applicant for infringement of the patent before the expiration of such period; and

(cc) in any case in which the notice provided under

paragraph (2)(B) relates to noninfringement, the notice was accompanied by a document described in subclause (III).

(II) Filing of civil action.—If the conditions described in items (aa), (bb), and as applicable, (cc) of subclause (I) have been met, the applicant referred to in such subclause may, in accordance with section 2201 of title 28, bring a civil action under such section against the owner or holder referred to in such subclause (but not against any owner or holder that has brought such a civil action against the applicant, unless that civil action was dismissed without prejudice) for a declaratory judgment that the patent is invalid or will not be infringed by the drug for which the applicant seeks approval, except that such civil action may be brought for a declaratory judgment that the patent will not be infringed only in a case in which the condition described in subclause (I)(cc) is applicable. A civil action referred to in this subclause shall be brought

in the judicial district where the defendant has its principal place of business or a regular and established place of business.

(III) Offer of confidential access to application.—For purposes of subclause (I)(cc), the document described in this subclause is a document providing an offer of confidential access to the application that is in the custody of the applicant referred to in subsection (b)(2) of this section for the purpose of determining whether an action referred to in subparagraph (C) should be brought. The document providing the offer of confidential access shall contain such restrictions as to persons entitled to access, and on the use and disposition of any information accessed, as would apply had a protective order been entered for the purpose of protecting trade secrets and other confidential business information. A request for access to an application under an offer of confidential access shall be considered acceptance of the offer of confidential access with the

restrictions as to persons entitled to access, and on the use and disposition of any information accessed, contained in the offer of confidential access, and those restrictions and other terms of the offer of confidential access shall be considered terms of an enforceable contract. Any person provided an offer of confidential access shall review the application for the sole and limited purpose of evaluating possible infringement of the patent that is the subject of the certification under subsection (b)(2)(A)(iv) of this section and for no other purpose, and may not disclose information of no relevance to any issue of patent infringement to any person other than a person provided an offer of confidential access. Further, the application may be redacted by the applicant to remove any information of no relevance to any issue of patent infringement.

(ii) Counterclaim to infringement action.—

(I) In general.—If an owner of the patent or the holder of the approved

application under subsection (b) of this section for the drug that is claimed by the patent or a use of which is claimed by the patent brings a patent infringement action against the applicant, the applicant may assert a counterclaim seeking an order requiring the holder to correct or delete the patent information submitted by the holder under subsection (b) of this section or this subsection on the ground that the patent does not claim either—

(aa) the drug for which the application was approved; or

(bb) an approved method of using the drug.

(II) No independent cause of action.—Subclause (I) does not authorize the assertion of a claim described in subclause (I) in any civil action or proceeding other than a counterclaim described in subclause (I).

(iii) No damages.—An applicant shall not be entitled to damages in a civil action under clause (i) or a counterclaim under clause (ii).

Appendix F

(E)(i) If an application (other than an abbreviated new drug application) submitted under subsection (b) of this section for a drug, no active ingredient (including any ester or salt of the active ingredient) of which has been approved in any other application under subsection (b) of this section, was approved during the period beginning January 1, 1982, and ending on September 24, 1984, the Secretary may not make the approval of another application for a drug for which the investigations described in clause (A) of subsection (b)(1) of this section and relied upon by the applicant for approval of the application were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted effective before the expiration of ten years from the date of the approval of the application previously approved under subsection (b) of this section.

(ii) If an application submitted under subsection (b) of this section for a drug, no active ingredient (including any ester or salt of the active ingredient) of which has been approved in any other application under subsection (b) of this section, is approved after September 24, 1984, no application which refers to the drug for which the subsection (b) application was submitted and for which the investigations described in clause

(A) of subsection (b)(1) of this section and relied upon by the applicant for approval of the application were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted may be submitted under subsection (b) of this section before the expiration of five years from the date of the approval of the application under subsection (b) of this section, except that such an application may be submitted under subsection (b) of this section after the expiration of four years from the date of the approval of the subsection (b) application if it contains a certification of patent invalidity or noninfringement described in clause (iv) of subsection (b)(2)(A) of this section. The approval of such an application shall be made effective in accordance with this paragraph except that, if an action for patent infringement is commenced during the one-year period beginning forty-eight months after the date of the approval of the subsection (b) application, the thirty-month period referred to in subparagraph (C) shall be extended by such amount of time (if any) which is required for seven and

one-half years to have elapsed from the date of approval of the subsection (b) application.

(iii) If an application submitted under subsection (b) of this section for a drug, which includes an active ingredient (including any ester or salt of the active ingredient) that has been approved in another application approved under subsection (b) of this section, is approved after September 24, 1984, and if such application contains reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant, the Secretary may not make the approval of an application submitted under subsection (b) of this section for the conditions of approval of such drug in the approved subsection (b) application effective before the expiration of three years from the date of the approval of the application under subsection (b) of this section if the investigations described in clause (A) of subsection (b)(1) of this section and relied upon by the applicant for approval of the application were not conducted by or for the applicant and if the applicant has not obtained a right of

reference or use from the person by or for whom the investigations were conducted.

(iv) If a supplement to an application approved under subsection (b) of this section is approved after September 24, 1984, and the supplement contains reports of new clinical investigations (other than bioavailabilty[1] studies) essential to the approval of the supplement and conducted or sponsored by the person submitting the supplement, the Secretary may not make the approval of an application submitted under subsection (b) of this section for a change approved in the supplement effective before the expiration of three years from the date of the approval of the supplement under subsection (b) of this section if the investigations described in clause (A) of subsection (b)(1) of this section and relied upon by the applicant for approval of the application were not conducted by or for the applicant and if the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted.

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1. So in original. Probably should be "bioavailability".

(v) If an application (or supplement to an application) submitted under subsection (b) of this section for a drug, which includes an active ingredient (including any ester or salt of the active ingredient) that has been approved in another application under subsection (b) of this section, was approved during the period beginning January 1, 1982, and ending on September 24, 1984, the Secretary may not make the approval of an application submitted under this subsection and for which the investigations described in clause (A) of subsection (b)(1) of this section and relied upon by the applicant for approval of the application were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted and which refers to the drug for which the subsection (b) application was submitted effective before the expiration of two years from September 24, 1984.

(4) A drug manufactured in a pilot or other small facility may be used to demonstrate the safety and effectiveness of the drug and to obtain approval for the drug prior to manufacture of the drug in a larger facility, unless the Secretary makes a determination that a full scale production

facility is necessary to ensure the safety or effectiveness of the drug.

(d) Grounds for refusing application; approval of application; "substantial evidence" defined

If the Secretary finds, after due notice to the applicant in accordance with subsection (c) of this section and giving him an opportunity for a hearing, in accordance with said subsection, that (1) the investigations, reports of which are required to be submitted to the Secretary pursuant to subsection (b) of this section, do not include adequate tests by all methods reasonably applicable to show whether or not such drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof; (2) the results of such tests show that such drug is unsafe for use under such conditions or do not show that such drug is safe for use under such conditions; (3) the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug are inadequate to preserve its identity, strength, quality, and purity; (4) upon the basis of the information submitted to him as part of the application, or upon the basis of any other information before him with respect to such drug, he has insufficient information to determine whether such drug is safe for use under such conditions; or (5) evaluated on the basis of the information submitted to him as part of the application and any other information before him with respect to such drug, there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling thereof; or (6) the application failed to contain the

patent information prescribed by subsection (b) of this section; or (7) based on a fair evaluation of all material facts, such labeling is false or misleading in any particular; he shall issue an order refusing to approve the application. If, after such notice and opportunity for hearing, the Secretary finds that clauses (1) through (6) do not apply, he shall issue an order approving the application. As used in this subsection and subsection (e) of this section, the term "substantial evidence" means evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof. If the Secretary determines, based on relevant science, that data from one adequate and well-controlled clinical investigation and confirmatory evidence (obtained prior to or after such investigation) are sufficient to establish effectiveness, the Secretary may consider such data and evidence to constitute substantial evidence for purposes of the preceding sentence.

(e) Withdrawal of approval; grounds; immediate suspension upon finding imminent hazard to public health

The Secretary shall, after due notice and opportunity for hearing to the applicant, withdraw approval of an application with respect to any drug under this section if the Secretary finds (1) that clinical or other experience, tests, or other scientific data show that such drug is unsafe for use under

the conditions of use upon the basis of which the application was approved; (2) that new evidence of clinical experience, not contained in such application or not available to the Secretary until after such application was approved, or tests by new methods, or tests by methods not deemed reasonably applicable when such application was approved, evaluated together with the evidence available to the Secretary when the application was approved, shows that such drug is not shown to be safe for use under the conditions of use upon the basis of which the application was approved; or (3) on the basis of new information before him with respect to such drug, evaluated together with the evidence available to him when the application was approved, that there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling thereof; or (4) the patent information prescribed by subsection (c) of this section was not filed within thirty days after the receipt of written notice from the Secretary specifying the failure to file such information; or (5) that the application contains any untrue statement of a material fact: Provided, That if the Secretary (or in his absence the officer acting as Secretary) finds that there is an imminent hazard to the public health, he may suspend the approval of such application immediately, and give the applicant prompt notice of his action and afford the applicant the opportunity for an expedited hearing under this subsection; but the authority conferred by this proviso to suspend the approval of an application shall not be delegated. The Secretary may also, after due notice and opportunity for hearing to the applicant, withdraw the approval of an application submitted under subsection (b) or (j) of this section with respect to any drug

under this section if the Secretary finds (1) that the applicant has failed to establish a system for maintaining required records, or has repeatedly or deliberately failed to maintain such records or to make required reports, in accordance with a regulation or order under subsection (k) of this section or to comply with the notice requirements of section 360(k)(2) of this title, or the applicant has refused to permit access to, or copying or verification of, such records as required by paragraph (2) of such subsection; or (2) that on the basis of new information before him, evaluated together with the evidence before him when the application was approved, the methods used in, or the facilities and controls used for, the manufacture, processing, and packing of such drug are inadequate to assure and preserve its identity, strength, quality, and purity and were not made adequate within a reasonable time after receipt of written notice from the Secretary specifying the matter complained of; or (3) that on the basis of new information before him, evaluated together with the evidence before him when the application was approved, the labeling of such drug, based on a fair evaluation of all material facts, is false or misleading in any particular and was not corrected within a reasonable time after receipt of written notice from the Secretary specifying the matter complained of. Any order under this subsection shall state the findings upon which it is based.

APPENDIX G — 21 U.S.C. § 352(f)

TITLE 21—FOOD AND DRUGS
CHAPTER 9—FEDERAL FOOD, DRUG, AND COSMETIC ACT SUBCHAPTER V—DRUGS AND DEVICES
Part A—Drugs and Devices

Sec. 352. Misbranded drugs and devices

A drug or device shall be deemed to be misbranded—

* * *

(f) Directions for use and warnings on label

Unless its labeling bears (1) adequate directions for use; and (2) such adequate warnings against use in those pathological conditions or by children where its use may be dangerous to health, or against unsafe dosage or methods or duration of administration or application, in such manner and form, as are necessary for the protection of users, except that where any requirement of clause (1) of this paragraph, as applied to any drug or device, is not necessary for the protection of the public health, the Secretary shall promulgate regulations exempting such drug or device from such requirement. Required labeling for prescription devices intended for use in health care facilities or by a health care professional and required labeling for in vitro diagnostic devices intended for use by health care professionals or in blood establishments may be made available solely by electronic means, provided that the labeling complies with all applicable requirements of law, and that the manufacturer affords such users the opportunity to request the labeling in paper form, and after such request, promptly provides the requested information without additional cost.

APPENDIX H — PUB L. 87-781 SEC 202

PUBLIC LAW 87-781 - OCT. 10, 1962

EFFECT ON STATE LAWS

Sec. 202. Nothing in the amendments made by this Act to the Federal Food, Drug, and Cosmetic Act shall be construed as invalidating any provision of State law which would be valid in the absence of such amendments unless there is a direct and positive conflict between such amendments and such provision of State law.

APPENDIX I — 21 C.F.R. § 314.70

§ 314.70 Supplements and other changes to an approved application.

(a) *Changes to an approved application.*

(1) The applicant notify FDA about each change in each condition established in an approved application beyond the variations already provided for in the application. The notice is required to describe the change fully. Depending on the type of change, the applicant must notify FDA about it in a supplement under paragraph (b) or (c) of this section or by inclusion of the information in the annual report to the application under paragraph (d) of this section.

(2) The holder of an approved application under section 505 of the act must assess the effects of the change before distributing a drug product made with a manufacturing change.

(3) Notwithstanding the requirements of paragraphs (b) and (c) of this section, an applicant must make a change provided for in those paragraphs in accordance with a regulation or guidance that provides for a less burdensome notification of the change (for example, by submission of a supplement that does not require approval prior to distribution of the product or in an annual report).

(4) The applicant must promptly revise all promotional labeling and advertising to make it consistent with any labeling change implemented in accordance with paragraphs (b) and (c) of this section.

(5) Except for a supplement providing for a change in the labeling, the applicant must include in each supplement and amendment to a supplement providing for a change under paragraph (b) or (c) of this section a statement certifying that a field copy has been provided in accordance with § 314.440(a)(4).

(6) A supplement or annual report must include a list of all changes contained in the supplement or annual report. For supplements, this list must be provided in the cover letter.

(b) *Changes requiring supplement submission and approval prior to distribution of the product made using the change (major changes).*

(1) A supplement must be submitted for any change in the drug substance, drug product, production process, quality controls, equipment, or facilities that has a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of the drug product as these factors may relate to the safety or effectiveness of the drug product.

(2) These changes include, but are not limited to:

(i) Except those described in paragraphs (c) and (d) of this section, changes in the qualitative or quantitative formulation of the drug product, including inactive ingredients, or in the specifications provided in the approved application;

(ii) Changes requiring completion of studies in accordance with part 320 of this chapter to demonstrate the equivalence of the drug product to the drug product as manufactured without the change or to the reference listed drug;

(iii) Changes that may affect drug substance or drug product sterility assurance, such as changes in drug substance, drug product, or component sterilization method(s) or an addition, deletion, or substitution of steps in an aseptic processing operation;

(iv) Changes in the synthesis or manufacture of the drug substance that may affect the impurity profile and/or the physical, chemical, or biological properties of the drug substance;

(v) The following labeling changes:

(A) Changes in labeling, except those described in paragraphs (c)(6)(iii), (d)(2)(ix), or (d)(2)(x) of this section;

(B) If applicable, any change to a Medication Guide required under part 208 of this chapter, except for changes in the information specified in § 208.20(b)(8)(iii) and (b)(8)(iv) of this chapter.

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(vi) Changes in a drug product container closure system that controls the drug product delivered to a patient or changes in the type (e.g., glass to high density polyethylene (HDPE), HDPE to polyvinyl chloride, vial to syringe) or composition (e.g., one HDPE resin to another HDPE resin) of a packaging component that may affect the impurity profile of the drug product.

(vii) Changes solely affecting a natural product, a recombinant DNA-derived protein/polypeptide, or a complex or conjugate of a drug substance with a monoclonal antibody for the following:

(A) Changes in the virus or adventitious agent removal or inactivation method(s);

(B) Changes in the source material or cell line; and

(C) Establishment of a new master cell bank or seed.

(viii) Changes to a drug product under an application that is subject to a validity assessment because of significant questions regarding the integrity of the data supporting that application.

(3) The applicant must obtain approval of a supplement from FDA prior to distribution of a drug product made using

a change under paragraph (b) of this section. Except for submissions under paragraph (e) of this section, the following information must be contained in the supplement:

(i) A detailed description of the proposed change;

(ii) The drug product(s) involved;

(iii) The manufacturing site(s) or area(s) affected;

(iv) A description of the methods used and studies performed to assess the effects of the change;

(v) The data derived from such studies;

(vi) For a natural product, a recombinant DNA-derived protein/ polypeptide, or a complex or conjugate of a drug substance with a monoclonal antibody, relevant validation protocols and a list of relevant standard operating procedures must be provided in addition to the requirements in paragraphs (b)(3)(iv) and (b)(3)(v) of this section; and

(vii) For sterilization process and test methodologies related to sterilization process validation, relevant validation protocols and a list of relevant standard operating procedures must be provided in addition to the requirements in paragraphs (b)(3)(iv) and (b)(3)(v) of this section.

(4) An applicant may ask FDA to expedite its review of a supplement for public health reasons or if a delay in making the change described in it would impose an extraordinary hardship on the applicant. Such a supplement and its mailing cover should be plainly marked: "Prior Approval Supplement- Expedited Review Requested."

(c) *Changes requiring supplement submission at least 30 days prior to distribution of the drug product made using the change (moderate changes).*

(1) A supplement must be submitted for any change in the drug substance, drug product, production process, quality controls, equipment, or facilities that has a moderate potential to have an adverse effect on the identity, strength, quality, purity, or potency of the drug product as these factors may relate to the safety or effectiveness of the drug product. If the supplement provides for a labeling change under paragraph (c)(6)(iii) of this section, 12 copies of the final printed labeling must be included.

(2) These changes include, but are not limited to:

(i) A change in the container closure system that does not affect the quality of the drug product, except those described in paragraphs (b) and (d) of this section; and

(ii) Changes solely affecting a natural protein, a recombinant DNA-derived protein/polypeptide or a complex or conjugate of a drug substance with a monoclonal antibody, including:

(A) An increase or decrease in production scale during finishing steps that involves different equipment; and

(B) Replacement of equipment with that of a different design that does not affect the process methodology or process operating parameters.

(iii) Relaxation of an acceptance criterion or deletion of a test to comply with an official compendium that is consistent with FDA statutory and regulatory requirements.

(3) A supplement submitted under paragraph (c)(1) of this section is required to give a full explanation of the basis for the change and identify the date on which the change is to be made. The supplement must be labeled "Supplement—Changes Being Effected in 30 Days" or, if applicable under paragraph (c)(6) of this section, "Supplement—Changes Being Effected."

(4) Pending approval of the supplement by FDA, except as provided in paragraph (c)(6) of this section, distribution of the drug product made using the change may begin not less than 30 days after receipt of the supplement by FDA. The information listed in paragraphs (b)(3)(i) through (b)(3)(vii) of this section must be contained in the supplement.

(5) The applicant must not distribute the drug product made using the change if within 30 days following FDA's receipt of the supplement, FDA informs the applicant that either:

> (i) The change requires approval prior to distribution of the drug product in accordance with paragraph (b) of this section; or
>
> (ii) Any of the information required under paragraph (c)(4) of this section is missing; the applicant must not distribute the drug product made using the change until the supplement has been amended to provide the missing information.

(6) The agency may designate a category of changes for the purpose of providing that, in the case of a change in such category, the holder of an approved application may commence distribution of the drug product involved upon receipt by the agency of a supplement for the change. These changes include, but are not limited to:

> (i) Addition to a specification or changes in the methods or controls to provide increased assurance that the drug substance or drug product will have the characteristics of identity, strength, quality, purity, or potency that it purports or is represented to possess;
>
> (ii) A change in the size and/or shape of a container for a nonsterile drug product, except for solid dosage forms, without a change in the labeled

amount of drug product or from one container closure system to another;

(iii) Changes in the labeling to accomplish any of the following:

(A) To add or strengthen a contraindication, warning, precaution, or adverse reaction;

(B) To add or strengthen a statement about drug abuse, dependence, psychological effect, or overdosage;

(C) To add or strengthen an instruction about dosage and administration that is intended to increase the safe use of the drug product;

(D) To delete false, misleading, or unsupported indications for use or claims for effectiveness; or

(E) Any labeling change normally requiring a supplement submission and approval prior to distribution of the drug product that FDA specifically requests be submitted under this provision.

(7) If the agency disapproves the supplemental application, it may order the manufacturer to cease distribution of the drug product(s) made with the manufacturing change.

Appendix I

(d) *Changes to be described in an annual report (minor changes).*

(1) Changes in the drug substance, drug product, production process, quality controls, equipment, or facilities that have a minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of the drug product as these factors may relate to the safety or effectiveness of the drug product must be documented by the applicant in the next annual report in accordance with § 314.81(b)(2).

(2) These changes include, but are not limited to:

(i) Any change made to comply with a change to an official compendium, except a change described in paragraph (c)(2)(iii) of this section, that is consistent with FDA statutory and regulatory requirements.

(ii) The deletion or reduction of an ingredient intended to affect only the color of the drug product;

(iii) Replacement of equipment with that of the same design and operating principles except those equipment changes described in paragraph (c) of this section;

(iv) A change in the size and/or shape of a container containing the same number of dosage units for a nonsterile solid dosage form drug

product, without a change from one container closure system to another;

(v) A change within the container closure system for a nonsterile drug product, based upon a showing of equivalency to the approved system under a protocol approved in the application or published in an official compendium;

(vi) An extension of an expiration dating period based upon full shelf life data on production batches obtained from a protocol approved in the application;

(vii) The addition or revision of an alternative analytical procedure that provides the same or increased assurance of the identity, strength, quality, purity, or potency of the material being tested as the analytical procedure described in the approved application, or deletion of an alternative analytical procedure;

(viii) The addition by embossing, debossing, or engraving of a code imprint to a solid oral dosage form drug product other than a modified release dosage form, or a minor change in an existing code imprint;

(ix) A change in the labeling concerning the description of the drug product or in the information about how the drug product is supplied, that does not involve a change in the dosage strength or dosage form; and

(x) An editorial or similar minor change in labeling.

(3) For changes under this category, the applicant is required to submit in the annual report:

(i) A statement by the holder of the approved application that the effects of the change have been assessed;

(ii) A full description of the manufacturing and controls changes, including the manufacturing site(s) or area(s) involved;

(iii) The date each change was implemented;

(iv) Data from studies and tests performed to assess the effects of the change; and,

(v) For a natural product, recombinant DNA-derived protein/ polypeptide, complex or conjugate of a drug substance with a monoclonal antibody, sterilization process or test methodology related to sterilization process validation, a cross-reference to relevant validation protocols and/or standard operating procedures.

(e) *Protocols.* An applicant may submit one or more protocols describing the specific tests and studies and acceptance criteria to be achieved to demonstrate the lack of adverse effect for specified types of manufacturing changes on the identity, strength, quality, purity, and potency of the drug

product as these factors may relate to the safety or effectiveness of the drug product. Any such protocols, if not included in the approved application, or changes to an approved protocol, must be submitted as a supplement requiring approval from FDA prior to distribution of a drug product produced with the manufacturing change. The supplement, if approved, may subsequently justify a reduced reporting category for the particular change because the use of the protocol for that type of change reduces the potential risk of an adverse effect.

(f) *Patent information.* The applicant must comply with the patent information requirements under section 505(c)(2) of the act.

(g) *Claimed exclusivity.* If an applicant claims exclusivity under § 314.108 upon approval of a supplement for change to its previously approved drug product, the applicant must include with its supplement the information required under § 314.50(j).

APPENDIX J — PREAMBLE

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 201, 314, and 601

[Docket No. 2000N–1269]
(formerly Docket No. 00N–1269) RIN 0910–AA94

Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

* * *

D. Comments on Product Liability Implications of the Proposed Rule

In the proposal, FDA requested comments on the product liability implications of revising the labeling for prescription drugs.

(Comment 12) In comments, some manufacturers expressed concerns that, by highlighting selected information from the FPI to the exclusion of information not highlighted, they make themselves more vulnerable to product liability claims. Some of these comments also stated that the Highlights limitation statement, which states that Highlights does not contain all the information needed to prescribe a

drug safely and effectively and that practitioners should also refer to the FPI, would not constitute an adequate legal defense in a case alleging failure to provide adequate warning of a drug's risks.

Based on the agency's research and analysis in developing the prototype labeling that was the basis for the proposed rule (see comment 2), the agency has concluded that a labeling format that includes Highlights is more effective than a format that omits Highlights. In response to the comments and as discussed in the response to comment 35, FDA has taken steps to enhance the prominence of the Highlights limitation statement. FDA believes the statement will be effective in reminding prescribers that the information in the Highlights should not be relied on exclusively in making prescribing decisions and that it is important to consult the more detailed information in the FPI. We also believe that this limitation statement will help to ensure that the labeling will be considered in its entirety in any product liability action. FDA acknowledges the comment's concerns and, as discussed more fully in response to comment 13, believes that under existing preemption principles such product liability claims would be preempted.

(Comment 13) Some comments stated that the new format requirements might have product liability implications for drugs that are not subject to the new requirements. These comments expressed concern that labeling in the old format might be characterized by plaintiffs as inferior to labeling in the new format and, as a result, could be used as evidence that a manufacturer did not provide adequate warnings. They requested that the agency state in the final rule that FDA

approval of labeling, whether it be in the old or new format, preempts conflicting or contrary State law, regulations, or decisions of a court of law for purposes of product liability litigation.

FDA believes that under existing preemption principles, FDA approval of labeling under the act, whether it be in the old or new format, preempts conflicting or contrary State law. Indeed, the Department of Justice (DOJ), on behalf of FDA, has filed a number of amicus briefs making this very point. In order to more fully address the comments expressing concern about the product liability implications of revising the labeling for prescription drugs, we believe it would be useful to set forth in some detail the arguments made in those amicus briefs. The discussion that follows, therefore, represents the government's long standing views on preemption, with a particular emphasis on how that doctrine applies to State laws that would require labeling that conflicts with or is contrary to FDA-approved labeling.

Under the act, FDA is the expert Federal public health agency charged by Congress with ensuring that drugs are safe and effective, and that their labeling adequately informs users of the risks and benefits of the product and is truthful and not misleading. Under the act and FDA regulations, the agency makes approval decisions based not on an abstract estimation of its safety and effectiveness, but rather on a comprehensive scientific evaluation of the product's risks and benefits under the conditions of use prescribed, recommended, or suggested in the labeling (21 U.S.C. 355(d)). FDA considers not only complex clinical issues related to the use of the product in study populations, but

also important and practical public health issues pertaining to the use of the product in day-to-day clinical practice, such as the nature of the disease or condition for which the product will be indicated, and the need for risk management measures to help assure in clinical practice that the product maintains its favorable benefit-risk balance. The centerpiece of risk management for prescription drugs generally is the labeling which reflects thorough FDA review of the pertinent scientific evidence and communicates to health care practitioners the agency's formal, authoritative conclusions regarding the conditions under which the product can be used safely and effectively. FDA carefully controls the content of labeling for a prescription drug, because such labeling is FDA's principal tool for educating health care professionals about the risks and benefits of the approved product to help ensure safe and effective use. FDA continuously works to evaluate the latest available scientific information to monitor the safety of products and to incorporate information into the product's labeling when appropriate.

Changes to labeling typically are initiated by the sponsor, subject to FDA review, but are sometimes initiated by FDA. Under FDA regulations, to change labeling (except for editorial and other minor revisions), the sponsor must submit a supplemental application fully explaining the basis for the change (§§ 314.70 and 601.12(f) (21 CFR 314.70 and 601.12(f))). FDA permits two kinds of labeling supplements: (1) Prior approval supplements, which require FDA approval before a change is made (§§ 314.70(b) and 601.12(f)(1)); and (2) "changes being effected" (CBE) supplements, which

may be implemented before FDA approval, but after FDA notification (§§ 314.70(c) and 601.12(f)(2)). While a sponsor is permitted to add risk information to the FPI without first obtaining FDA approval via a CBE supplement, FDA reviews all such submissions and may later deny approval of the supplement, and the labeling remains subject to enforcement action if the added information makes the labeling false or misleading under section 502(a) of the act (21 U.S.C. 352). Thus, in practice, manufacturers typically consult with FDA prior to adding risk information to labeling. As noted in response to comment 5, however, a sponsor may not use a CBE supplement to make most changes to Highlights.

Since the proposed rule was published, FDA has learned of several instances in which product liability lawsuits have directly threatened the agency's ability to regulate manufacturer dissemination of risk information for prescription drugs in accordance with the act. In one case, for example, an individual plaintiff claimed that a drug manufacturer had a duty under California State law to label its products with specific warnings that FDA had specifically considered and rejected as scientifically unsubstantiated.[4] In some of these cases, the court determined that the State law claim could not proceed, on the ground that the claim was preempted by Federal law,[5] or was not properly before the

4. *Dowhal* v. *SmithKline Beecham Consumer Healthcare*, 2002 Cal. App. LEXIS 4384 (Cal. Ct. App. 2002), reversed, 2004 Cal. LEXIS 3040 (Cal. April 15, 2004).

5. *E.g.*, *Ehlis* v. *Shire Richwood, Inc.*, 233 F. Supp. 2d 1189, 1198 (D.N.D. 2002), *aff'd on other grounds*, 367 F.3d 1013 (8th Cir. 2004).

court by operation of the doctrine of primary jurisdiction.[6] In some cases, however, the court has permitted the claim to proceed.[7]

State law actions can rely on and propagate interpretations of the act and FDA regulations that conflict with the agency's own interpretations and frustrate the agency's implementation of its statutory mandate. For example, courts have rejected preemption in State law failure-to-warn cases on the ground that a manufacturer has latitude under FDA regulations to revise labeling by adding or strengthening warning statements without first obtaining permission from FDA. (*See, e.g., Eve* v. *Sandoz Pharm. Corp.*, 2002 U.S. Dist. LEXIS 23965 (S.D. In. Jan. 28, 2002); *Ohler* v. *Purdue Pharma, L.P.*, 2002 U.S. Dist. LEXIS 2368 (E.D. La. Jan. 22, 2002); *Motus* v. *Pfizer Inc.*, 127 F. Supp.

6. *E.g., Bernhardt* v. *Pfizer, Inc.*, 2000 U.S. Dist. LEXIS 16963 (S.D.N.Y. Nov. 16, 2000). This doctrine allows a court to refer a matter to an administrative agency for an initial determination where the matter involves technical questions of fact and policy within the agency's jurisdiction. If a court finds that the agency has primary jurisdiction, the court stays the matter and instructs the plaintiff to initiate an action with the agency. *See, e.g., Israel* v. *Baxter Labs., Inc.*, 466 F.2d 272, 283 (D.C. Cir. 1972); see also 21 CFR 10.60.

7. *Dowhal* v. *SmithKline Beecham Consumer Healthcare*, 2002 Cal. App. LEXIS 4384 (Cal. Ct. App. 2002), *reversed*, 2004 Cal. LEXIS 3040 (Cal. April 15, 2004); *Bernhardt* v. *Pfizer, Inc.*, 2000 U.S. Dist. LEXIS 16963 (S.D.N.Y. November 16, 2000); *Motus* v. *Pfizer, Inc.*, 127 F. Supp. 2d 1085 (C.D. Cal. 2000), summary judgment granted, 196 F. Supp. 2d 984, 986 (C.D. Cal. 2001), aff'd, 2004 U.S. App. LEXIS 1944 (9th Cir. February 9, 2004); *In re Paxil Litigation*, 2002 U.S. Dist. LEXIS 16221 (C.D. Cal. August 16, 2002), transferred, 296 F. Supp. 2d 1374 (J.P.M.L. 2003).

2d 1085 (C.D. Cal. 2000); *Bansemer* v. *Smith Labs., Inc.*, 1988 U.S. Dist. LEXIS 16208 (E.D. Wis. Sept. 12, 1988); *McEwen* v. *Ortho Pharm Corp.*, 528 P.2d 522 (Ore. 1974).) In fact, the determination whether labeling revisions are necessary is, in the end, squarely and solely FDA's under the act. A manufacturer may, under FDA regulations, strengthen a labeling warning, but in practice manufacturers typically consult with FDA before doing so to avoid implementing labeling changes with which the agency ultimately might disagree (and that therefore might subject the manufacturer to enforcement action).

Another misunderstanding of the act encouraged by State law actions is that FDA labeling requirements represent a minimum safety standard. According to many courts, State law serves as an appropriate source of supplementary safety regulation for drugs by encouraging or requiring manufacturers to disseminate risk information beyond that required by FDA under the act. (*See, e.g.*, *Brochu* v. *Ortho Pharm. Corp.*, 642 F.2d 652 (1st Cir. 1981); *Salmon* v. *Parke-Davis and Co.*, 520 F.2d 1359 (4th Cir. 1975); *Caraker* v. *Sandoz Pharm. Corp.*, 172 F. Supp. 2d 1018 (S.D. Ill. 2001); *Mazur* v. *Merck & Co., Inc.*, 742 F. Supp. 239 (E.D. Pa. 1990); *In re Tetracycline Cases*, 747 F. Supp. 543 (W.D. Mo. 1989).) In fact, FDA interprets the act to establish both a "floor" and a "ceiling," such that additional disclosures of risk information can expose a manufacturer to liability under the act if the additional statement is unsubstantiated or otherwise false or misleading. Given the comprehensiveness of FDA regulation of drug safety, effectiveness, and labeling under the act, additional requirements for the disclosure of risk information are not necessarily more protective of patients. Instead, they can erode and disrupt the careful and truthful

representation of benefits and risks that prescribers need to make appropriate judgments about drug use. Exaggeration of risk could discourage appropriate use of a beneficial drug.

State law requirements can undermine safe and effective use in other ways. In the preamble accompanying the proposal, FDA noted that liability concerns were creating pressure on manufacturers to expand labeling warnings to include speculative risks and, thus, to limit physician appreciation of potentially far more significant contraindications and side effects (65 FR 81082 at 81083). FDA has previously found that labeling that includes theoretical hazards not wellgrounded in scientific evidence can cause meaningful risk information to "lose its significance" (44 FR 37434 at 37447, June 26, 1979). Overwarning, just like underwarning, can similarly have a negative effect on patient safety and public health. (See section X of this document.) Similarly, State-law attempts to impose additional warnings can lead to labeling that does not accurately portray a product's risks, thereby potentially discouraging safe and effective use of approved products or encouraging inappropriate use and undermining the objectives of the act. (*See, e.g., Dowhal* v. *SmithKline Beecham Consumer Healthcare*, 2002 Cal. App. LEXIS 4384 (Cal. Ct. App. 2002) (allowing to proceed a lawsuit involving a California State law requiring warnings in the labeling of nicotine replacement therapy products that FDA had specifically found would misbrand the products under the act), reversed, 2004 Cal. LEXIS 3040 (Cal. April 15, 2004).)

State law actions also threaten FDA's statutorily prescribed role as the expert Federal agency responsible for

evaluating and regulating drugs. State actions are not characterized by centralized expert evaluation of drug regulatory issues. Instead, they encourage, and in fact require, lay judges and juries to second-guess the assessment of benefits versus risks of a specific drug to the general public—the central role of FDA—sometimes on behalf of a single individual or group of individuals. That individualized reevaluation of the benefits and risks of a product can result in relief—including the threat of significant damage awards or penalties—that creates pressure on manufacturers to attempt to add warnings that FDA has neither approved nor found to be scientifically required. This could encourage manufacturers to propose "defensive labeling" to avoid State liability, which, if implemented, could result in scientifically unsubstantiated warnings and underutilization of beneficial treatments.

FDA has previously preempted State law requirements relating to drugs in rulemaking proceedings. For example:

• In 1982, FDA issued regulations requiring tamper-resistant packaging for OTC drugs. In the preamble accompanying the regulations, FDA stated its intention that the regulations preempt any State or local requirements that were "not identical to * * * [the rule] in all respects" (47 FR 50442 at 50447, November 5, 1982).

• In 1986, FDA issued regulations requiring aspirin manufacturers to include in labeling a warning against use in treating chicken pox or flu symptoms in children due to the risk of Reye's Syndrome. In the accompanying preamble, FDA said the regulations preempted "State and local

packaging requirements that are not identical to it with respect to OTC aspirin-containing products for human use" (51 FR 8180 at 8181, March 7, 1986).

• In 1994, FDA amended 21 CFR 20.63 to preempt State requirements for the disclosure of adverse event-related information treated as confidential under FDA regulations (59 FR 3944, January 27, 1994). (See also 47 FR 54750, December 3, 1982) ("FDA believes that differing State OTC drug pregnancy-nursing warning requirements would prevent accomplishment of the full purpose and objectives of the agency in issuing the regulation and that, under the doctrine of implied preemption, these State requirements are preempted by the regulation as a matter of law.")

As noted previously, DOJ has made submissions to courts in a number of cases in which private litigants asserted a State law basis for challenging the adequacy of risk information provided by manufacturers for drugs in accordance with FDA requirements under the act. In each case, DOJ argued that the doctrine of preemption precluded the plaintiff's claim from proceeding.[8] The practice of

8. The DOJ submissions in these cases relied on the doctrine of implied preemption or primary jurisdiction. Although the act itself contains no general express pre-emption provision for drugs, a provision of legislation amending the drug provisions addresses the relationship of the legislation to State law. Section 202 of the Drug Amendments of 1962 (Public Law 87-781, Title II, section 202, 76 Stat. 793 (October 10, 1962)) provides: "Nothing in the amendments made by this Act to the Federal Food, Drug, and Cosmetic Act shall be construed as invalidating any provision of State law which would

(Cont'd)

addressing conflicting State requirements through participation in litigation (including product liability cases) in which the Government is not a party is not new. For example, DOJ participated on FDA's behalf in favor of pre-emption in *Jones* v. *Rath Packing Company*, 430 U.S. 519 (1977), *Grocery Manufacturers of America, Inc.* v. *Gerace*, 755 F.2d 993 (2d Cir. 1985), *Eli Lilly & Co., Inc.* v. *Marshall*, 850 S.W.2d 155 (Tex. 1993), and *Buckman Co.* v. *Plaintiffs' Legal Comm.*, 531 U.S. 341, 352–53 (2001). FDA believes that State laws conflict with and stand as an obstacle to achievement of the full objectives and purposes of Federal law when they purport to compel a firm to include in labeling or advertising a statement that FDA has considered and found scientifically unsubstantiated. In such cases, including the statement in labeling or advertising would render the drug misbranded under the act (21 U.S.C. 352(a) and (f)). The agency believes that State law conflicts with and stands as an obstacle to achievement of the full objectives and purposes of Federal law if it purports to preclude a firm from including in labeling or advertising a statement that is included in prescription drug labeling. By complying with the State law in such a case and removing the statement from labeling, the firm would be omitting a statement required under § 201.100(c)(1) as a condition on the exemption from the requirement of adequate directions for use, and the omission

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(Cont'd)

be valid in the absence of such amendments unless there is a direct and positive conflict between such amendments and such provision of State law." The existence of a legislative provision addressing pre-emption does not bar the operation of ordinary principles of implied preemption (*Geier* v. *American Honda Motor Co., Inc.*, 529 U.S. 861, 869 (2000)).

would misbrand the drug under 21 U.S.C. 352(f)(1). The drug might also be misbranded on the ground that the omission is material within the meaning of 21 U.S.C. 321(n) and makes the labeling or advertising misleading under 21 U.S.C. 352(a) or (n).

Consistent with its court submissions and existing preemption principles, FDA believes that at least the following claims would be preempted by its regulation of prescription drug labeling. (1) Claims that a drug sponsor breached an obligation to warn by failing to put in Highlights or otherwise emphasize any information the substance of which appears anywhere in the labeling; (2) claims that a drug sponsor breached an obligation to warn by failing to include in an advertisement any information the substance of which appears anywhere in the labeling, in those cases where a drug's sponsor has used Highlights consistently with FDA draft guidance regarding the "brief summary" in direct-to-consumer advertising ("Brief Summary: Disclosing Risk Information in Consumer-Directed Print Advertisements," 69 FR 6308 (February 2004)) (see comment 112); (3) claims that a sponsor breached an obligation to warn by failing to include contraindications or warnings that are not supported by evidence that meets the standards set forth in this rule, including § 201.57(c)(5) (requiring that contraindications reflect "[k]nown hazards and not theoretical possibilities") and (c)(7); (4) claims that a drug sponsor breached an obligation to warn by failing to include a statement in labeling or in advertising, the substance of which had been proposed to FDA for inclusion in labeling, if that statement was not required by FDA at the time plaintiff claims the sponsor had an obligation to warn (unless FDA has made a finding that the sponsor withheld material information relating to the proposed warning

before plaintiff claims the sponsor had the obligation to warn); (5) claims that a drug sponsor breached an obligation to warn by failing to include in labeling or in advertising a statement the substance of which FDA has prohibited in labeling or advertising; and (6) claims that a drug's sponsor breached an obligation to plaintiff by making statements that FDA approved for inclusion in the drug's label (unless FDA has made a finding that the sponsor withheld material information relating to the statement). Preemption would include not only claims against manufacturers as described above, but also against health care practitioners for claims related to dissemination of risk information to patients beyond what is included in the labeling. (See, e.g., *Bowman* v. *Songer*, 820 P.2d 1110 (Col. 1991).)

FDA recognizes that FDA's regulation of drug labeling will not preempt all State law actions. The Supreme Court has held that certain State law requirements that parallel FDA requirements may not be preempted (*Medtronic, Inc.* v. *Lohr*, 518 U.S. 470, 495 (1996) (holding that the presence of a State law damages remedy for violations of FDA requirements does not impose an additional requirement upon medical device manufacturers but ''merely provides another reason for manufacturers to comply with * * * federal law''); id. at 513 (O'Connor, J., concurring in part and dissenting in part); id)). *But see Buckman Co.* v. *Plaintiffs' Legal Comm.*, 531 U.S. 341, 352–53 (2001) (holding that "fraud on the FDA" claims are preempted by Federal law); 21 U.S.C. 337(a) (restricting the act enforcement to suits by the United States); *In re Orthopedic Bone Screw Prods. Liability Litig.*, 159 F.3d 817, 824 (3d Cir. 1998) (''Congress has not created an express or implied private cause of action for violations of the FDCA or the MDA [Medical Device Amendments]'').

* * * *

APPENDIX K — REGULATORY HISTORY

INTERNAL CORRESPONDENCE

William E. Langeland, Ph.D.

Company WLD located Radnor

Subject Phenergan® Advere Reaction
Lt. Colonel Harry Cerha
Headquarters, AFMSTC
Washington, D.C. 20333

From Walter H. Comer, M.D.

Company WLD located Radnor

Date February 17, 1967

Dear Bill:

Lt. Colonel Harry Cerha informed us of an adverse reaction occurring in a woman during labor involving three drugs given intravenously in a single injection. These drugs are Demerol®, Leritine® and Phenergan. A severe arteriospasm resulted during the injection, with pain and cyanosis observed in the arm. In spite of recognized, acceptable treatment, the spasm continued, resulting in gangrene of the arm and subsequent amputation.

The information from Colonel Cerha was given in a phone conversation February 15, 1967, and is not complete. The incident occurred some time in 1965. This information is being presented to the Food and Drug Administration

Appendix K

because it is the first such incident reported to us involving Phenergan.

Phenergan was given (50 mg.) IV in a dose not recommended in the approved Phenergan direction circular. The direction circular also gives warning against perivascular extravasation and also includes a warning against intra - arterial injection.

Information reached us because of an allegation on the part of the patient against the Air Force.

Sincerely,

s/ Walter H. Comer
Walter H. Comer, M.D.

WHC: jda

Enclosure – Drug Reaction Report

Appendix K

DEPARTMENT OF HEALTH, EDUCATION,
AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
ROCKVILLE, MARYLAND

NDA 8-857/S-005

Wyeth Laboratories
Attention: Earl T. Lewis, M.D.
P. O. Box 8299
Philadelphia, Pennsylvania 19101 May 4, 1976

Gentlemen:

Reference is made to your supplemental new drug application of November 14, 1975 submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for PHENERGAN® (promethazine hydrochloride) Injection.

The supplemental application provides for a revised package insert as discussed in our conference of August 25, 1975 and in our letter of August 29, 1975.

We have completed review of this supplemental application as submitted with draft labeling. In order to furnish adequate information for the safe use of the drug, the following revisions in the labeling should be made:

* * *

Appendix K

D. WARNINGS

* * *

5. The last paragraph as it appears on page three of the draft labeling should be modified as follows: the statement "when used intravenously, promethazine hydrochloride should be given in a concentration no greater than 25 mg per cc. and at a rate not too exceed 25 mg per minute," should be deleted and removed to the DOSAGE AND ADMINISTRATION section. Preceding the remainder of the paragraph the following statement should appear, all in caps: "ASPIRATION OF DARK BLOOD DOES NOT PRECLUDE INTRA-ARTERIAL NEEDLE PLACEMENT AS BLOOD IS DISCOLORED UPON CONTACT WITH PROMETHAZINE." The remainder of the paragraph is acceptable.

* * *

F. ADVERSE REACTIONS:

* * *

2. The paragraph entitled "Cardiovascular Effects" should be revised. This paragraph should be rewritten as follows: "Postural hypotension is the most common

cardiovascular effect of promethazine. Reflex tachycardia associated with mild increases in blood pressure have been seen with the use of promethazine hydrochloride. Bradycardia, faintness, dizziness and EKG changes, including blunting of T waves and prolongation of the Q-T INTERVAL may be seen. INTERARTERIAL INJECTION MAY RESULT IN GANGRENE OF THE AFFECTED EXTREMITY."

* * *

Please submit your revised labeling in draft form for our review.

Sincerely yours,
Margaret A. Clark, M.D.
Director
Division of Surgical-Dental
Drug Products
Bureau of Drugs

Appendix K

FOOD AND DRUG ADMINISTRATION
BUREAU OF DRUGS
ANESTHESIOLOGY ADVISORY COMMITTEE
EIGHTEENTH MEETING

October 14, 1976

Teakwood Suite
The San Francisco Hilton
Mason and O'Farrell Streets
San Francisco, California

MEMBERS OF THE ADVISORY COMMITTEE PRESENT:

Betty J. Ramforth, M.D. - Chairman
Philip R. Bromege, M.S.
Burnell R. Brown, Jr., M.D., Ph.D.
Helmut F. Cascorbi, M.D., Ph.D.
Athole G. Jacobi, M.D.
Kenneth Sugioka, M.D.

MEMBERS OF THE ADVISORY COMMITTEE ABSENT:

M. Robert Knapp, M.D.

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BUREAU OF DRUGS PERSONNEL IN ATTENDANCE:

Gerald M. Rachanow, Executive Secretary
Margaret A. Clark, M.D., HFD-160
Patricia H. Russell, M.D., HFD-160
David L. Scally, M.D., HFD-160

PUBLIC ATTENDEES:

Jeffrey M. Baden - Stanford, California
Harold H. Borgstodt, M.D. - Rochester, New York
Terrell A. Crowley, Ph.D. - North Chicago, Illinois
Edmond I. Eger, II, M.D. - San Francisco, California
Louis L. Ferstandig, Ph.D. - Hackensack, New Jersey
Ben Hitt, Ph.D. - Stanford, California
Duncan A. Holaday, M.D. - Miami, Florida
John B. Jewell, M.D. - New York, New York
Richard I. Mazze, N.D. - Stanford, California
James L. McNahon - New York, New York
William A. Hischel - Lexington, Massachusetts
W. D. Northcroft - San Mateo, California
James L. Ryan - Santa Ana, California
Charles W. Simons - Lexington, Massachusetts
Bradley E. Smith, M.D. - Nashville, Tennessee
Ross C. Terrell - New Providence, New Jersey
James F. Vitcha - Cape Coral, Florida

ANESTHESIOLOGY ADVISORY COMMITTEE

The meeting was called to order at 9:00 A.M., Dr. Betty J. Bamforth, Chairman, presiding. Dr. Athole G. Jacobi, the newest Committee member, was introduced.

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OPEN PUBLIC HEARING:

An opportunity was provided for members of the public present to make comments or ask questions relevant to the Advisory Committee's agenda or other work, and no comments or questions were presented.

OPEN COMMITTEE DISCUSSION:

* * *

The second item on the agenda was the proposed package insert revision for Phenergan (promethazine hydrochloride) Injection, NDA 8-857, The FDA has proposed that the first paragraph of the CONTRAINDICATIONS section of the package insert be revised to state: "Promethazine is contraindicated in comatose states, in patients who have received large amounts of central nervous system depressants (alcohol, barbiturates, narcotics, etc.), in patients who have bone marrow depression, and in patients who have demonstrated an idiosyncrasy or hypersensitivity to promethazine." The manufacturer, Wyeth Laboratories, disagrees with the contraindication to the use of Phenergan Injection in bone marrow depression. The question presented to the Advisory Committee was whether "Based on the limited case reports of blood dyscrasias which have been received, should the use of Phenergan Injection be contraindicated in bone marrow depression? or would a WARNING statement be more appropriate at this time?" The Committee agreed that present evidence does not warrant a contraindication, but that it certainly warrants a warning.

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The FDA medical officer had suggested that since arterial injection is not an acceptable means of administering drugs that the second paragraph of the CONTRAINDICATIONS section (concerning intra-arterial injection) be deleted. Wyeth Laboratories has stated its strong feeling that this contraindication to the intra-arterial injection of Phenergan is entirely appropriate in its present location and is essential to ensure the safe use of this drug. The question presented to the Advisory Committee was "Should the reference to intra-arterial injection remain or be deleted from the CONTRAINDICATIONS section?" The Committee agreed that it had no objections to including this statement under CONTRAINDICATIONS and that, because of the seriousness of the problem, statements concerning intra-arterial injection which appear in the WARNINGS section should remain there also.

One of the Committee members commented that the present statement (i.e., Subcutaneous injection is not recommended; . . .) concerning subcutaneous injection was pretty mild and that this statement should be made stronger or should appear in the CONTRAINDICATIONS section because there have been at least three or four cases of abscesses developing because of subcutaneous injection of the drug. He added that tissue necrosis and slough may follow subcutaneous injection and that the drug should be given by deep intra-muscular injection. The Committee agreed that an additional paragraph should be added to the CONTRAINDICATIONS section stating that Phenegan Injection should not be given by subcutaneous injection (because of the possibility of

abscesses developing and of tissue necrosis) and that deep intra-muscular injection is the recommended route of administration of the drug.

* * *

The Committee was also asked: "Since it appears that it may be difficult to aspirate or be aware of intra-arterial pressure when using Wyeth's Tubex system to administer this drug and that more intra-arterial injections occur when the Tubex system is used is used in place of a plain needle and syringe, should the use of Tubex be discussed in this section (or perhaps in the PRECAUTIONS section)?" The Committee agreed that the following statement should be added under the Parenteral Administration subsection of the WARNINGS section: "If a Tubex system is used for intravenous injection, the drug should be injected into a satisfactorily functioning intravenous set."

* * *

The next meeting was tentatively scheduled for March 1977. The meeting adjourned at 2:45 P.M.

I certify that I attended the eighteenth meeting of the Anesthesiology Advisory Committee of the Food and Drug Administration cn October 14, 1976, and that these minutes accurately reflect what transpired.

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Chairman s/ Betty J. Bamforth
Betty J. Bamforth, M.D.

Executive Secretary s/ Gerald K. Rachanow
Gerald M. Rachanow

Appendix K

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

MAR 26, 1987

NDA 8-957/5-009

Wyeth Laboratories
P.O. Box 8299
Philadelphia, PA 19101

Attention: Paul V. Uses
Associate Director
Drug Regulatory Affairs

Gentlemen:

Please refer to your supplemental new drug application dated September 21, 1981 (S-009) submitted pursuant to section 505(b) of the Federal Food, Drug and Cosmetic Act for Phenegan (promthazine HCl) Injection.

The supplemental application provides for revised labeling to conformance with the Labeling Format Revision Program (21 CFR 201.56 and 201.57).

Reference is also made to the agency letter dated November 5, 1984, requesting further revisions in the labeling. We have

not yet received a response to the referenced letter. The following comments, most of which were conveyed to you by Dr. D. Scally, should be incorporated in the revised labeling. Please note that the comments include some deficiencies which were noted in S-012 dated November 13, 1986, as well as those noted in the original labeling supplement dated September 21, 1981.

The labeling should be revised as follows:

* * *

WARNINGS

Please revise your WARNINGS discussion of Inadvertent Intra-arterial Injection according to the following text:

> "INADVERTENT INTRA-ARTERIAL INJECTION: There are reports of necrosis leading to gangrene, requiring amputation, following injection of promethazine, usually in conjunction with other drugs; the intravenous route was intended in these cases, but arterial or partial arterial placement of the needle is now suspect. The mechanism is uncertain, however, animal experiments with other arteriolar irritants suggests that the initiating factor may be platelet aggregation and thrombosis starting distal to the site of injection.
>
> "The first sign may be the patient's reaction to a sensation of fiery burning, roughly following the

distribution path of the injected artery; no more drug should be injected until the situation is remedied. Blanching may be present early, may be transient or may not be noted at all. Blotchy dynosis and dark discoloration usually follows.

"There is no established treatment other than prevention:

1. Beware of the close proximity of arteries and veins at commonly used injection sites and consider the possibility of aberrant arteries.

2. When used intravenously, promethazine hydrochloride should be given in a concentration no greater than 25 mg/ml and at a rate not to exceed 25 mg/minute. Injection through a properly running intravenous infusion may enhance the possibility of detecting arterial placement. In addition, this results in delivery of a lower concentration of any arteriolar irritant.

3. Subcutaneous swelling near the site of injection calls for discontinuation of promethazine administration and reevaluation of the situation. This sign may be

indicative of venous extravasion, which may result in localized necrosis, or it may signify partial arterial placement of needle or catheter.

4. Beware *that the characteristic bright-red color of arterial blood is discolored by contact with promethazine.* (Italics or different print underlined.)

"Post injury injection of vasodilators an/or arterial infusion of parenteral fluids are generally regarded as being of no value in altering outcome. Animal experiments and published individual case reports concerned with a variety of arteriolar irritants suggests that one or more of the following *may* be a benefit in reducing the area of necrosis:

1. Arterial injection of heparin at the site of injury, followed by systemic anticoagulation.

2. Sympathetic blood (or brachial plexus block in the arm), if anticoagulant therapy permits.

3. Intra-arterial gluocorticoid injection at the site of injury, followed by systemic steroids.

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4. A recent case report (non-promethazine drug injury) suggests that intra-arterial urokinase may promote fibrinolysis, even if administered late in treatment."

The references supporting the above discussion are:

1. G.S. Buckspan, et al., Intraarterial Drug Injury: Studies of Etiology and Potential Treatment. JL. SURG. RES. 24(4): 294-301, 1978.

2. W.P. Wiedeman, et al., *In Vivo* Microscopic Observations of Intra-Arterial Injections of Barbiturates, JL. SURG. RES. 22(2): 94-108, 1977.

3. S.S. Brown, et al., Intra-Arterial Barbiturates, BRIT. JL. ANAES. 40: 13-19, 1968.

4. J.S. Mathers & E. Goodhead, Intra-arterial Methohexitone and Thiopentone, ANAESTHESIA 21(1): 81-89, 1966.

5. G.A. Webb & N. Lampert, Accidental Arterial Injections. AM. J. OBST. & GYNEC. 101(3): 365-371, 1 June 1968.

6. H.S. Engler, et al., Production of Gangrenous Extremeties by Intra-Arterial Injections, AMERICAN SURGEON 30(9): 602-607, Sept. 1964.

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7. D.L. Hager & J.N. Wilson, Gangrene of the Hand Following Intra-Arterial Injection, ARCH. SURG. 94: 86-89, Jan. 1967.

8. R.F. Lynas & W.I.K. Bisset, Intra-Arterial Thiopentone, ANAESTHESIA 24(2): 257-261, April 1969.

9. G. Corser, et al., Ischamia Following Self Administered Intra-Arterial Injection of Methylphenidate and Diamorphine, ANAESTHESIA 40: 51-54, 1985

10. D.J. Waters, Intra-Arterial Thiopental, ANAESTHESIA 21(3): 346-356, July 1966.

11. Correspondence Regarding Thiopental and Thiamylal (3 Letters): 1. L.C. Mark, 2. J.W. Dundee, 3. S. Dohi & M. Naito. ANESTHESIOLOGY 59: 153-155, 1983.

12. D. Albo, K. Reemtsma, et al., Effect of Intra-Arterial Injections of Barbiturates, AMERICAN JL. OF SURGERY 120: 676-678, November 1970.

13. E.C. Klatte, et al., Toxicity of Intra-Arterial Barbiturates and Tranquilizing Drugs, RADIOLOGY 92(4) 92(4): 700-704, March 1969.

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14. M.L. Nahrwold, et al., Inadvertent Intra-Arterial Injection of Mephenteramine, ROCKY MOUNTAIN MEDICAL JOURNAL, 70(9): 38-39, September 1973.

15. G. Enloe, et al., Hazards of Intra-Arterial Injection of Hydroxyzine, CANADIAN ANAES. SOC. JL. 16(5): 425-428, September 1969.

16. H.S. Engler, et al., Gangrenous Extremities Resulting from Intra-Arterial Injections, ARCH. SURG. 94: 644-651, May 1967.

17. J.B. Kinmonth & R.C. Shephard, Accidental Injection of Thiopentone Into Arteries, Studies of Pathology and Treatment, BRITISH MEDICAL JOURNAL, 2: 914-918, 1959.

18. D. Goldsmith & N. Trieger, Accidental Intra-Arterial Injection: A Medical Emergency, ANESTHESIA PROGRESS 226): 180-183, Nov.-Dec. 1975.

19. R. Miller, et al., Intra-Arterial Injection of a Barbiturate — A Case Report, ANESTHESIA PROGRESS 23(1): 25-27, Jan.-Feb. 1976.

20. H.H. Stone & C.C. Donnelly, REVIEW ARTICLE, The Accidental Intra-Arterial Injection of Thiopental, ANESTHESIOLOGY 22: 995-1006, 1961.

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* * *

Please submit revised draft labeling as soon as possible.

Sincerely yours,
s/ [illegible]
Patricia H. Russell, M.D.
Acting Director
Division of Surgical-Dental
Drug Products
Office of Drug Research and Review
Center for Drugs and Biologics

Appendix K

CONFIDENTIAL

WYETH
AYERST

INTERNAL CORRESPONDENCE

to: File
from: James O'Shaughnessy
company: W-AR located 170/2
subject: Phenergan® Injection Pending Supplements
date: January 30, 1997

On January 29, 1997, I spoke with Ms. Beverly Gallauresi of the Division of Pulmonary Drug Products (DPDP) regarding the following pending supplemental applications for Phenergan Injection.

NDA No. 8-857/S-009
Labeling Supplement

This supplement was initially filed in 1981. There have been numerous amendments and submissions of draft labeling and supportive documentation over the years. In June 1996, Wyeth-Ayerst was asked to prepare a narrative outlining the differences in the text of the currently approved package insert and any text changes since 1992. During the remainder of 1996, the DPDP consistently advised that the labeling review was nearing an end.

During today's conversation, Ms. Gallauresi indicated that the labeling review is complete. However, because it has taken the DPDP so long to complete the review, they are

taking extra care to make sure they have dotted every "i" and crossed every "t." She advised me that a letter is circulating within the DPDP for final review and comments. Ms. Gallauresi said she hoped this letter could be FAXed to us in the very near future, however, she could not guarantee that this would happen before Friday, February 7, 1997.

Appendix K

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

FEB 21 1997

CONFIDENTIAL

NDA 8-857/5-009

Wyeth-Ayerst
P.O. Box 8299
Philadelphia, PA 19101-8299

Attention: James J. O'Shaughnessy
Associate Director
U.S. Regulatory Affairs

Dear Mr. O'Shaughnessy:

Reference is made to your supplemental new drug application dated September 21 1981, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Phenergan (promethazine hydrochloride) Injection.

We acknowledge receipt of your amendments dated May 3, 1988, February 1, March 1, and May 15, 1989, January 7, 1992, and August 6, 1996.

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We have completed the review of this supplemental application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to submit final printed labeling (FPL) revised as follows.

The following comments are provided regarding the versions of the Phenergan Tubex and Ampul labeling submitted in the August 6, 1996 amendment. Please note that the term "current labeling" refers to these versions.

1. Identical inserts should be utilized for both Phenergan Tubex and Phenergan Ampuls, except for description and usage information specific to the Tubex Sterile Cartridge Unit and the sulfite warning, which is specific to the ampul formulation.

2. The format for the trade name should be "Phenergan (promethazine HCL) Injection" and should be used consistently for both the tubex and ampul products. Within the package inserts, the term "promethazine hydrochloride" or "promethazine HCL" is appropriate for the DESCRIPTION and the CLINICAL PHARMACOLOGY

* * *

10. The WARNINGS section should be modified to read as follows.

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* * *

f. Inadvertent Intra-arterial Injection - Retain verbiage in current label.

* * *

15. The DOSAGE AND ADMINISTRATION section should be modified as follows,

a. The sentence which ends ". . . without some hazard." should be followed by "Not for subcutaneous administration."

b. The sentence which begins "Inadvertent intra-arterial injection . . ." should appear in bold. The statement which follows, regarding rate of administration, should be offset in a separate paragraph.

* * *

16. Regarding the tubex product, the instructions for use refer to a "Tubex injector." This device should be described in the HOW SUPPLIED section.

17. Both Ampuls and Tubex boxes, 25 and 50 mg strength, should describe route of injection as 25 mg - IV or IM, 50 mg - IM only.

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Please submit 16 copies of the printed labeling, ten of which are individually mounted on heavy-weight paper or similar material.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Within 10 days after the date of this letter, you are required to amend the supplemental application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of such action FDA may take action to withdraw the application.

If you have any questions, please contact Ms. Beverly Gallauresi, Project Manager, at (301) 827-1054.

Sincerely yours,

s/ John K. Jenkins, M.D.
Director
Division of Pulmonary Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Appendix K

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

SEP 18 1998

NDA 8-857/S-009

Wyeth-Ayerst Laboratories
P.O. Box 8299
Philadelphia, PA 19101-8299

Attention: Nanette E. Holston
Manager
U.S. Regulatory Affairs

Dear Ms. Holston:

Please refer to your supplemental new drug application dated September 21, 1981, received September 21, 1981, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Phenergan (promethazine hydrochloride) Injection, 25 and 50 mg/mL.

We acknowledge receipt of your submissions dated May 3, 1988, February 1, March 1, and May 15, 1989, January 7, 1992, August 6, 1996, and May 8 and August 21, 1998. Your submission of May 8, 1998, constituted a full response to our February 21, 1997, action letter.

Appendix K

This supplemental new drug application provides for revised labeling.

We have completed the review of this supplemental application, including the draft package insert dated May 8, 1998, and the final printed carton and container labels dated August 21, 1998, and it is approved effective on the date of this letter.

The final printed labeling (FPL) for the package insert must be identical to the draft package insert submitted May 8, 1998.

Please submit 20 copies of the FPL for the package insert as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement 8-857/S-009" Approval of this submission by FDA is not required before the labeling is used.

If additional information relating to the safety or effectiveness of this drug becomes available before we receive the final printed labeling, revision of the labeling may be required.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

Appendix K

If you have any questions, contact Mr. David Hilfiker, Project Manager, at (301) 827-1046.

Sincerely yours,

s/ John K. Jenkins
John K. Jenkins, M.D., F.C.C.P.
Director
Division of Pulmonary Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

APPENDIX L — CURRENT LABEL

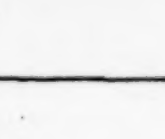
Injection
CI 3727-7

BEST AVAILABLE COPY

Phenergan®
(promethazine HCl)
Injection

DESCRIPTION

Phenergan (promethazine HCl) Injection is a sterile, pyrogen-free solution for deep intramuscular or intravenous administration. Promethazine HCl (10H-phenothiazine-10-ethanamine, *N,N,α*-trimethyl-, monohydrochloride, (±)-) is a racemic compound and has the following structural formula:



$C_{17}H_{20}N_2S \cdot HCl$ MW=320.89

Each mL of the PHENERGAN and PHENERGAN PLAINT PHENTE™ Double Cartridge Units contains either 25 or 50 mg promethazine HCl with 0.1 mg edetate disodium, 0.04 mg sodium sulfoxylate, and more than 5 mg monothioglycerol, and 5 mg phenol as buffer for injection. The pH range is 4.0 to 5.5, buffered with sodium acetate-acetic acid, and it is packed under nitrogen.

Phenergan (promethazine HCl) Injection is a clear, colorless solution. The product is light sensitive. It should be inspected before use and discarded if either color or particulate is observed.

CLINICAL PHARMACOLOGY

Promethazine HCl is a phenothiazine derivative which possesses antihistaminic, sedative, antimotion-sickness, antiemetic, and anticholinergic effects. Promethazine is a competitive H1 receptor antagonist, but does not block the release of histamine. Structural differences from the neuroleptic phenothiazines result in the relative lack (1/10) of dopamine antagonism properties. In therapeutic doses, promethazine HCl produces an appreciable effect on the cardiovascular system. Clinical effects are generally apparent within 5 minutes of an intravenous injection and within 20 minutes of an intramuscular injection. Duration of action is four to six hours, although effects may persist up to 12 hours. Promethazine HCl is metabolized in the liver, with the formation of promethazine sulfoxide and N-demethylpromethazine being the predominant metabolites appearing in the urine. Following intravenous administration in healthy volunteers, the plasma half-life for promethazine has been reported to range from 9 to 16 hours. The mean plasma half-life for promethazine after intramuscular administration in healthy volunteers has been reported to be 5.0 ± 3.4 hours.

INDICATIONS AND USAGE

Phenergan Injection is indicated for the following conditions:

1. Amelioration of allergic reactions to blood or plasma.
2. As adjunctive to or adjunct to epinephrine and other standard measures after the acute symptoms have been controlled.
3. For other uncomplicated allergic conditions of the immediate type when oral therapy is impossible or contraindicated.
4. For sedation and relief of apprehension and to produce light sleep from which the patient can be easily aroused.
5. Active treatment of motion sickness.
6. Prevention and control of nausea and vomiting associated with certain types of anesthesia and surgery.
7. As an adjunct to analgesics for the control of postoperative pain.
8. Preoperative, postoperative, and obstetric (during labor) sedation.
9. Intravenously in special surgical situations, such as repeated bronchoscopy, ophthalmic surgery, and post-vitrectomy patients, with reduced amounts of meperidine or other narcotic analgesic as an adjunct to anesthesia and analgesia.

CONTRAINDICATIONS

Phenergan Injection is contraindicated in comatose states and in patients who have demonstrated an idiosyncrasy or hypersensitivity to antihistamines or other phenothiazines.

Since an extravascular product Phenergan Injection has given by intra-arterial injection due to the likelihood of severe arteriospasm and the possibility of resultant gangrene (see "WARNINGS—Intravenous and Intra-arterial Injection").

Phenergan Injection should not be given by the subcutaneous route, because of observed irritation has been noted, and necrotic lesions have resulted on rare occasions following subcutaneous injection. The preferred parenteral route of administration is by deep intramuscular injection.

WARNINGS

CNS Depression

Phenergan Injection may impair the mental and physical abilities required for the performance of potentially hazardous tasks, such as driving a vehicle or operating machinery. The impairment may be amplified by concomitant use of other central-nervous-system depressants such as alcohol, barbiturates, narcotics, tranquilizers, general anesthetics, narcotic analgesics, antipsychotics, etc. (see "PRECAUTIONS—Information for Patients").

Lower Seizure Threshold

Phenergan Injection may lower seizure threshold and should be used with caution in persons with seizure disorders or in persons who are using concomitant medications, such as narcotics or local anesthetics, which may also affect seizure threshold.

Bone-Marrow Depression

Phenergan Injection should be used with caution in persons with bone-marrow depression. Leukopenia and agranulocytosis have been reported, usually when Phenergan has been used in association with other known marrow-toxic agents.

Use in Pediatric Patients

PHENERGAN INJECTION IS NOT RECOMMENDED FOR USE IN PEDIATRIC PATIENTS LESS THAN TWO YEARS OF AGE.

CAUTION SHOULD BE EXERCISED WHEN ADMINISTERING PHENERGAN INJECTION TO PEDIATRIC PATIENTS 2 YEARS OF AGE AND OLDER. ANTIEMETICS ARE NOT RECOMMENDED FOR TREATMENT OF UNCOMPLICATED VOMITING IN PEDIATRIC PATIENTS, AND THEIR USE SHOULD BE LIMITED TO HIGH-DOSED VOMITING OF KNOWN ETIOLOGY. THE EXTRAPYRAMIDAL SYMPTOMS WHICH CAN OCCUR SECONDARY TO PHENERGAN INJECTION ADMINISTRATION MAY BE CONFUSED WITH THE CNS SIGNS OF UNDIAGNOSED PRIMARY DISEASE, E.G., ENCEPHALOPATHY OR REYE'S SYNDROME. THE USE OF PHENERGAN INJECTION SHOULD BE AVOIDED IN PEDIATRIC PATIENTS WHOSE SIGNS AND SYMPTOMS MAY SUGGEST REYE'S SYNDROME OR OTHER HEPATIC DISEASE.

Excessively large dosages of antihistamines, including Phenergan Injection, in pediatric patients may cause hallucinations, convulsions, and sudden death. In pediatric patients who are usually ill associated with dehydration, there is an increased susceptibility to dystonias with the use of Phenergan Injection.

Intra-arterial Intra-arterial Injection

Due to the close proximity of arteries and veins in the areas most commonly used for intravenous injection, extreme care should be exercised to avoid unintended administration of intravenous intra-arterial injection. Reports compatible with unintended intra-arterial injection of Phenergan Injection usually in combination with other drugs intended for intravenous use, indicated that pain, severe chemical irritation, severe spasm of distal vessels, and resultant gangrene requiring amputation may rarely occur such circumstances. Intravenous injection was intended in all the cases reported but precautions for administration or related assessment of the results were lacking. There is no proven therapeutic management of this syndrome after it occurs, although sympathetic block and hyperbaric oxygen are commonly employed during the acute pathophysiologic sequelae of the results of arterial experiments, with other known arterial injuries. Addition of 25 mg Phenergan Injection with 4 mg of procaine hydrochloride, 1 mg heparin, and 1 mg hydrocortisone per 100 mL of normal saline solution has been reported to prevent these complications.

Phenergan Injection should be given in a concentration not greater than 25 mg per mL and at a rate not to exceed 25 mg per minute. When administering any enteral drug intravenously, it is usually preferable to inject it through the tubing of an intravenous infusion set that is known to be functioning satisfactorily, in the event that a patient complains of pain during intravenous injection of Phenergan Injection, the injection should be stopped immediately to provide for evaluation of possible arterial puncture or perivascular extravasation.

Visual Inspection

This product is light sensitive and should be inspected before use and discarded if either color or particulate is observed.

Other Considerations

Sedative drugs or CNS depressants should be avoided in patients with a history of drug abuse.

Administration of promethazine has been associated with reported diabetotic jaundice.

PRECAUTIONS

General

Drugs having antihistaminic properties should be used with caution in patients with narrow-angle glaucoma, prostatic hypertrophy, stenosing peptic ulcer, pyloroduodenal obstruction, and bladder-neck obstruction.

Phenergan Injection should be used cautiously in persons with cardiovascular disease or impairment of liver function.

Information for Patients

Phenergan Injection may cause marked drowsiness or impair the mental or physical abilities required for the performance of potentially hazardous tasks, such as driving a vehicle or operating machinery. The use of alcohol, narcotics, barbiturates (including barbiturates), general anesthetics, narcotic analgesics, tranquilizers, etc. with Phenergan Injection may additively compound. Patients should be instructed to avoid potential harm in this effect or in other hazardous activities.

Patients should be advised to report any involuntary dystonic movements.

Persistent or worsening pain or burning at the injection site should be reported immediately.

Avoid prolonged exposure to the sun.

Drug Interactions

CNS Depressants - Phenergan Injection may potentiate, additively or synergistically, the sedative effects of central-nervous-system depressants, such as alcohol, sedative-hypnotics (including barbiturates), general anesthetics, narcotics, narcotic analgesics, tranquilizers, etc. When given concomitantly with Phenergan Injection, the dose of barbiturates should be reduced by at least one-half, and the dose of narcotics should be reduced by one-quarter to one-half. Dosage should be reconsidered if excessive amounts of Phenergan Injection relieve pain in a patient. May lead to restlessness and motor hyperactivity in the patient with pain; these symptoms usually disappear with adequate control of the pain.

Epinephrine - Although reversal of the vasopressor effect of epinephrine has not been reported with Phenergan Injection, it is recommended that epinephrine NOT be used in the case of Phenergan Injection overdose.

Antihistamines - Concomitant use of other agents with antihistaminic properties should be undertaken with caution.

Monoamine Oxidase Inhibitors (MAOI) - Drug interactions, including an increased incidence of extrapyramidal effects, have been reported when some MAOI and phenothiazines are used concomitantly. Although such a reaction has not been reported with Phenergan Injection, the possibility should be considered.

Laboratory Test Interactions

The following laboratory tests may be affected in patients who are receiving therapy with Phenergan Injection:

Pregnancy Tests - Diagnostic pregnancy tests based on immunological reactions between HCG and anti-HCG may result in false-negative or false-positive interpretations.

Glucose Tolerance Test - An increase in glucose tolerance has been reported in patients receiving promethazine HCl.

Carcinogenesis, Mutagenesis and Impairment of Fertility

Long-term animal studies have not been performed to evaluate the carcinogenic potential of Phenergan Injection, nor are there other sources of human data concerning carcinogenicity, mutagenicity, or impairment of fertility. Phenergan Injection was nonmutagenic in the Ames, Escherichia coli system.

Pregnancy

Teratogenic Effects—Pregnancy Category C

Teratogenic effects have not been demonstrated in rat feeding studies at doses of 6.25 and 12.5 mg/kg (approximately 2.1 and 4.2 times the maximum recommended human daily dose) of Phenergan Injection. Daily doses of 25 mg/kg intramuscularly have been found to produce fetal mortality in rats.

There are no adequate and well-controlled studies of Phenergan Injection in pregnant women. Because animal reproduction studies are not always predictive of human response, Phenergan Injection should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Adequate studies to determine the effect of the drug on parturition, lactation and development of the animal neonate have not been conducted.

Abnormogenic Effects

Phenergan Injection flattened within two weeks of delivery may exhibit platelet aggregation in the newborn.

Labor and Delivery

Phenergan Injection may be used alone or as an adjunct to narcotic analgesics during labor (see "DOSAGE AND ADMINISTRATION"). Limited data suggest that use of Phenergan Injection during labor and delivery does not have an appreciable effect on the duration of labor or delivery and does not increase the risk of need for intervention in the newborn. The effect on later growth and development of the newborn is unknown. (See also "Teratogenic Effects.")

Nursing Mothers

It is not known whether Phenergan Injection is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Phenergan Injection is administered to a nursing woman.

Pediatric Use

Safety and effectiveness in pediatric patients under 2 years of age have not been established.

Phenergan Injection should be used with caution in pediatric patients 2 years of age and older (see "WARNINGS—Use in Pediatric Patients").

Use in Geriatric Patients (approximately 60 years or older)

Safety studies with clinical experience have not been performed in geriatric patients. However, the dosage should be reduced for these patients.

ADVERSE REACTIONS

CNS Effects

Drowsiness is the most frequent CNS effect of this drug. Disorientation has also been observed, especially in elderly patients. Confusion, excitation, and hyperreflexia may occur, especially in children. Dizziness, vertigo, blurred vision, fixation of gaze, and tinnitus have been reported.

Cardiovascular Effects

Hypotension, tachycardia, bradycardia, and palpitations have been reported following the use of Phenergan Injection. Rarely, cardiac arrest has occurred following intra-arterial injection of promethazine HCl.

Appendix L

[illegible] ARE [illegible] OF THE AFFECTED

[illegible]

Cardiovascular Effects

[illegible] have been reported, usually in association with surgical procedures and some [illegible] drug therapy.

Allergic Reactions

[illegible] urticaria, pruritus, edema, and anaphylactoid. Angioneurotic edema has been reported.

Other Reported Reactions

Leukopenia and agranulocytosis, usually when Phenergan has been used in association with [illegible] other drugs, have been reported. Thrombophlebitis, necrosis and jaundice of the obstructive type have been associated with the use of Phenergan. The jaundice is usually reversible on discontinuation of the drug. Subcutaneous injection has resulted in tissue necrosis. Acute hemolytic [illegible] has been reported.

Paradoxical Reactions (Overdosage)

Hyperexcitability and convulsive movements, which have been reported in pediatric patients following [illegible] administration of Phenergan injection, may be manifestations of relative overdosage, or [illegible] idiosyncrasy. Caution should be given to the discontinuation of Phenergan injection and to the use of other drugs. Respiratory depression, hypotension, delirium, and agitated behavior have also been reported in spite of these episodes.

OVERDOSAGE

Signs and symptoms of overdosage range from mild depression of the central nervous system and cardiovascular system to profound hypotension, respiratory depression, and unresponsiveness.

Convulsions may be evident, especially in pediatric patients and geriatric patients. Convulsions may rarely occur. A paradoxical reaction has been reported in pediatric patients receiving single doses of 75 mg to 125 mg orally, characterized by hyperexcitability and restlessness.

Recognize the signs and symptoms — dry mouth, [illegible], dilated pupils, flushing, etc., as well as [illegible] exaggerated symptomatic, may occur.

Treatment

Treatment of overdosage is essentially symptomatic and supportive. Only in cases of extreme overdosage or [illegible] satisfactorily do vital signs, including respiration, pulse, blood pressure, temperature, and EKG, need to be monitored. Attention should be given to the reestablishment of adequate respiratory exchange through provision of a patent airway and intubation of assisted or controlled ventilation. Oxygen may be used to control cyanosis. Analeptics and pressor/vasopressor agents should be avoided. Note that any depressant effects of Phenergan injection are not reversed by naloxone.

Gastric evacuation, which may cause convulsions. The treatment of choice for reducing hypotension is administration of intravenous fluids, supplemented by vasopressors if indicated. In the event that vasopressors are considered for the management of severe hypotension, [illegible] may be required to overcome fluid and vasodilation. The administration of levarterenol or metaraminol should be considered. EPINEPHRINE SHOULD NOT BE USED, since its use in a person with partial parasympathetic blockade may further lower the blood pressure. Extrapyramidal reactions may be treated with antihistaminic preparations, diphenylhydramine, or barbiturates. Oxygen may also be administered. Limited experience with dialysis indicates that it is not helpful.

DOSAGE AND ADMINISTRATION

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Do not use Phenergan injection if solution has developed color or contains precipitate.

To avoid the possibility of physical drug incompatibility, consult specialized literature before diluting with any injectable solution or combining with any other medication. Do not use if there is a precipitate or any sign of incompatibility.

Important Notes on Administration

The preferred parenteral route of administration for Phenergan injection is by deep intramuscular injection. The proper intramuscular administration of this product is well-established, but one of the risks is that certain nerve injury, [illegible] postinjection administration.

[illegible] INTRA-ARTERIAL INJECTION CAN RESULT IN GANGRENE OF THE AFFECTED EXTREMITY (see "WARNINGS—Intra-arterial Injection"). SUBCUTANEOUS INJECTION IS CONTRAINDICATED, AS IT MAY RESULT IN TISSUE NECROSIS (see "CONTRAINDICATIONS").

Injection into or near a nerve may result in permanent tissue damage.

When used intravenously, Phenergan injection should be given in concentration no greater than 25 mg/mL at a rate not to exceed 25 mg per minute, it is permissible to inject through the tubing of an intravenous infusion set that is known to be functioning satisfactorily.

The TUBEX® BLUNT POINTE™ Sterile Cartridge Unit is suitable for substances to be administered intramuscularly. It is intended for use with injection units specifically manufactured as "needle-less" injection systems. As of the date of this update, the TUBEX BLUNT POINTE is compatible with LifeShield® Protected Needle injection site, InterLink® Injection Site, SmartLine® Injection Site, Clave® Needleless Injection Cap, and SafeSite® valve valve".

The TUBEX® Sterile Cartridge-Needle Unit is suitable for substances to be administered intramuscularly or subcutaneously.

Dosage Guidelines

The average adult dose is 25 mg. This dose may be repeated within two hours if necessary, but repeated therapy, if indicated, should be on the oral route as soon as evening antiemetic permit. After initiation of treatment, dosage should be adjusted to the smallest amount adequate to relieve symptoms. The average adult dose for sedation of elderly patients is 25 mg.

Sedation

In hospitalized adult patients, nighttime sedation may be achieved by a dose of 25 to 50 mg of Phenergan injection.

Nausea and Vomiting

For control of nausea and vomiting, the usual adult dose is 12.5 to 25 mg, not to be repeated more frequently than every four hours. When used for control of postoperative nausea and vomiting, the medication may be administered either intramuscularly or intravenously and dosage of analgesics and barbiturates reduced accordingly.

Preoperative and Postoperative Use

As an adjunct to preoperative or postoperative medication, 25 to 50 mg of Phenergan injection in adults may be combined with appropriately reduced doses of analgesics and [illegible] drugs as desired. Dosage of concomitant analgesic or hypnotic medication should be reduced accordingly.

Obstetrics

Phenergan injection in doses of 50 mg will provide sedation and relieve apprehension in the early stages of labor. When labor is definitely established, 25 to 75 mg (in single doses, 50 mg) Phenergan injection may be given intramuscularly or intravenously with an appropriately reduced dose of any desired narcotic. If necessary, Phenergan injection with a reduced dose of analgesic may be repeated once or twice at four-hour intervals in the course of a normal labor. A maximum total dose of 100 mg of Phenergan injection may be administered during a 24-hour period to patients in labor.

Pediatric Patients

Phenergan injection is not recommended for use in pediatric patients less than two years of age.

In pediatric patients 2 years of age and older, the dosage should not exceed half that of the suggested adult dose. As an adjunct to premedication, the suggested dose is 0.5 mg per lb. of body weight in combination with an appropriately reduced dose of narcotic or barbiturate and the appropriate dose of an atropine-like drug. Antiemetics should not be used in vomiting of unknown etiology in pediatric patients (see "WARNINGS—Use in Pediatric Patients").

HOW SUPPLIED

Phenergan® (promethazine HCl) injection is available in the following dosage strengths in TUBEX® BLUNT POINTE™ Sterile Cartridge Units and Sterile Cartridge-Needle Units, packaged in boxes of 10 TUBEX® as follows:

25 mg per mL, NDC 0008-0410-50, 1 mL box BLUNT POINTE™
25 mg per mL, NDC 0008-0410-01, 1 mL box (22 gauge x 1-1/4 inch needle).
50 mg per mL, NDC 0008-0417-01, 1 mL box (22 gauge x 1-1/4 inch needle).

TUBEX® BLUNT POINTE™ Sterile Cartridge Units and Sterile Cartridge-Needle Units are intended for use with the TUBEX® Injector, which is a reusable plastic injector designed for administration of these products.

Store at room temperature, between 15°C-25°C (59°F-77°F).
Protect from light. Keep carton until time of use.
Do not use if solution has developed color or contains a precipitate.

Also available:

Phenergan Injection is also available in 1 mL ampuls, in packages of 25 ampuls, as follows:

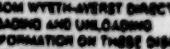
25 mg per mL, NDC 0008-0053-01.
50 mg per mL, NDC 0008-0746-01.

PLEASE NOTE: THE WYETH-AYERST METAL TUBEX HYPODERMIC SYRINGE AND TUBEX FAST-TRAK SYRINGE HAVE BEEN DISCONTINUED AND REPLACED BY THE TUBEX INJECTOR. EXCHANGE OF THESE DISCONTINUED SYRINGES IS AVAILABLE, FREE OF CHARGE, FROM YOUR WYETH-AYERST SALES REPRESENTATIVE, OR FROM WYETH-AYERST DIRECTLY. FOR LOADING AND UNLOADING INFORMATION ON THESE DISCONTINUED SYRINGES, CONTACT THE MEDICAL AFFAIRS DEPARTMENT AT WYETH-AYERST LABORATORIES, P.O. BOX 8299, PHILADELPHIA, PA 19101.

TUBEX® Injector

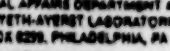
NOTE: The TUBEX Injector is REUSABLE; do not discard.

TUBEX Sterile Cartridge-Needle Unit DIRECTIONS FOR USE:



TUBEX® BLUNT POINTE™ Sterile Cartridge Unit

DIRECTIONS FOR USE:



TUBEX BLUNT POINTE Sterile Cartridge Unit is intended for use with injection units specifically manufactured as "needle-less" injection systems. As of the date of this update, TUBEX BLUNT POINTE Sterile Cartridge Unit is compatible with LifeShield® Protected Needle injection site, InterLink® Injection Site, SmartLine® Injection Site, Clave® Needleless Injection Cap, and SafeSite® valve valve".

Consult manufacturer's recommendations regarding "Directions for Use" of the "needle-less" injection system.

NOTE: USE ASEPTIC TECHNIQUE FOR ALL MANIPULATIONS OF STERILE PARTS.

To load a TUBEX Sterile Cartridge Unit into the TUBEX Injector

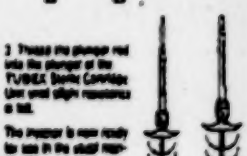
1. Turn the ribbed collar to the "OPEN" position until it stops.

TUBEX Sterile Cartridge-Needle Unit

TUBEX BLUNT POINTE Sterile Cartridge Unit

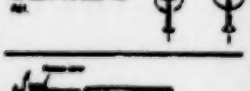
2. Hold the Injector with the open end up and fully insert the TUBEX Sterile Cartridge Unit.

Firmly tighten the ribbed collar in the direction of the "CLOSE" arrow.

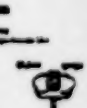


3. Thread the plunger rod into the plunger of the TUBEX Sterile Cartridge Unit until slight resistance is felt.

The Injector is now ready for use in the usual manner.



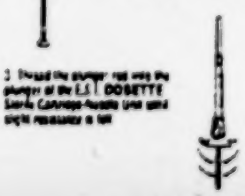
To load an E.S.I. DOSETTE® Sterile Cartridge-Needle Unit into the TUBEX Injector



1. Turn the ribbed collar to the "OPEN" position until it stops.

2. Hold the Injector with the open end up and fully insert the E.S.I. DOSETTE Sterile Cartridge-Needle Unit.

Firmly tighten the ribbed collar in the direction of the "CLOSE" arrow.



3. Thread the plunger rod into the plunger of the E.S.I. DOSETTE Sterile Cartridge-Needle Unit until slight resistance is felt.

4. Engage the needle tab assembly by pushing the tab down over the barrel cartridge hub. The needle is fully engaged when the lower hub is completely covered.

The Injector is now ready for use in the usual manner.

To administer TUBEX/DOSETTE Sterile Cartridge-Needle Units

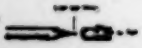
Instead of administering in the same as with conventional syringe. Remove needle cover by grasping it securely, twist and pull. Administer by pushing needle into patient, as per by pushing skin slightly on the plunger, and inject.

To administer TUBEX BLUNT POINTE Sterile Cartridge Units

"Needle-less" IV

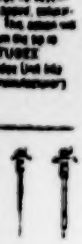
Set administration

A better to administer with conventional syringe.



Remove rubber cover by grasping it securely, twist and pull. "For Safety" notice when securely seats the Luer slip fitting of the TUBEX BLUNT POINTE Sterile Cartridge to accessory with a sterile, individually wrapped, solution of 70% isopropyl alcohol pads. This action will remove the sterile sealing from the tip of [illegible] a right seal. Attached TUBEX BLUNT POINTE Sterile Cartridge Unit into the "needle-less" IV set as per manufacturer's "Directions for Use."

To remove the empty TUBEX/DOSETTE Cartridge Unit and dispose into a vertical disposal container



1. Do not recap the needle point. Disengage the plunger rod

2. Hold the Injector, needle/point down, over a vertical disposal container and loosen the ribbed collar.

TUBEX/DOSETTE Cartridge Unit will drop into the container.

3. Discard the cover.

To remove the empty TUBEX/DOSETTE Cartridge Unit and dispose into a horizontal enclosed disposal container

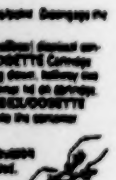
1. Do not recap the needle/point. Disengage the plunger rod

2. Open the horizontal enclosed disposal container. Insert TUBEX/DOSETTE Cartridge Unit, needle/point pointing down, halfway into container. Close the container lid on syringe. Loosen ribbed collar. TUBEX/DOSETTE Cartridge Unit will drop into the container.

3. Discard the cover.

The TUBEX Injector is reusable and should not be discarded.

Used TUBEX/DOSETTE Cartridge Units should not be considered for successive treatment or as multiple-dose containers. They are intended to be used only once and discarded.



NOTE: Any proposed markings on TUBEX/DOSETTE Sterile Cartridge Units are to be used only as a guide in administering dosage. Wyeth-Ayerst does not recommend and will not assume responsibility for the use of any cartridge-needle units or medications safety other than TUBEX or E.S.I. DOSETTE Cartridge Units in the TUBEX Injector.

TUBEX is a registered trademark of Wyeth-Ayerst Laboratories. BLUNT POINTE is a trademark of Wyeth-Ayerst Laboratories.

[illegible] is a registered trademark of Sterile Corporation, Inc.

[illegible] is a registered trademark of Abbott Laboratories.

[illegible] is a registered trademark of Becton, Dickinson & Company.

[illegible] is a registered trademark of Baxter Healthcare Corporation.

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Supreme Court, U.S.
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No. 06-1249

IN THE
Supreme Court of the United States

WYETH,

Petitioner,

v.

DIANA LEVINE,

Respondent.

On Petition for a Writ of Certiorari to the Supreme Court of Vermont

RESPONDENT'S BRIEF IN OPPOSITION

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April 2007

QUESTION PRESENTED

The Vermont Supreme Court below affirmed an award of compensatory damages to respondent Diana Levine. As the case comes to this Court, petitioner Wyeth does not challenge that, as a matter of Vermont law, Ms. Levine's arm was amputated because Wyeth failed to warn against using a method of administering its anti-nausea drug Phenergan that causes precisely the type of injury that Ms. Levine sustained.

The question presented is

Should this Court grant review to consider whether the Food and Drug Administration's approval of the labeling for Phenergan impliedly preempts the award of compensatory damages to Ms. Levine where

(a) no appellate court has ever adopted the position advanced by Wyeth;

(b) the Vermont Supreme Court found, as a matter of fact, that the FDA never considered, let alone rejected, a warning to preclude use of the method of administration that caused Ms. Levine's injuries;

(c) an FDA regulation permits a drug manufacturer, without FDA approval, to revise an existing label to "add or strengthen an instruction about dosage or administration that is intended to increase the safe use of the drug"; and

(d) the 2006 FDA regulatory preamble on which Wyeth relies for its claim of preemption does not, by its terms, apply to the circumstances of this case, and was not issued until *after* the FDA approved the label at issue here?

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INTRODUCTION

On April 7, 2000, respondent Diana Levine, a professional musician, went to the hospital for treatment of a headache and, after being injected with a drug manufactured by petitioner Wyeth, left with injuries that led quickly and irreversibly to the loss of her right arm. Specifically, Ms. Levine's arm had to be amputated because Wyeth's drug Phenergan, prescribed to alleviate nausea associated with a migraine headache, reached Ms. Levine's arteries. Wyeth knew that arterial contact causes the exact injuries Ms. Levine sustained. Phenergan was given to Ms. Levine using a method of administration that was consistent with, and not precluded by, Wyeth's label instructions and that Wyeth knew risked contact with Ms. Levine's arteries. Because Wyeth did not warn against that method of administration in its drug labeling or otherwise, a Vermont jury awarded Ms. Levine compensatory damages, and the Vermont Supreme Court affirmed.

The question presented by Wyeth – whether the Food and Drug Administration's approval of a prescription drug label preempts state-law damages actions premised on "differing labeling judgments" – is not worthy of review for a fundamental reason embodied in this Court's Rule 10: Although the FDA's drug approval process and the states' traditional common-law civil justice systems have co-existed for nearly 70 years, not a single federal or state appellate court has ever held that a state-law failure-to-warn verdict is preempted by the federal laws governing the marketing and labeling of prescription drugs. To the contrary, every appellate court to have addressed the question has held that a state-law damages claim based on a drug manufacturer's failure to warn is not preempted by federal law.

Moreover, even if the Court were inclined to consider the question presented by Wyeth, *this case* does not present it. Wyeth's petition is premised on the factual assertion that the

FDA specifically considered and rejected a warning on the method of administration for Phenergan that Ms. Levine claimed would have prevented her injuries. The purported differences between the FDA's commands with respect to Phenergan's label and the duty-to-warn that Ms. Levine claimed entitled her to damages created, in Wyeth's view, an impermissible conflict between federal and state law. But Wyeth's factual claim is simply not accurate. The Vermont Supreme Court held, *as a matter of fact*, that Wyeth's assertions regarding FDA's label decisions were unsupported by "any evidence," Pet. App. 16a, and that the record contained no basis for Wyeth's claim that the FDA had considered, let alone rejected, the warning that Ms. Levine claimed would have prevented her injuries. *See id.* at 17a-19a. The Vermont Supreme Court's understanding of the factual record is correct, and, in any event, this Court should not grant review to consider a legal issue that would only be reached if the Court were first to overturn a state court's factual determinations.

This case is an inappropriate vehicle for considering the question presented for another reason as well. Wyeth rests its preemption argument in large part on the purported preemptive power of an FDA regulatory preamble issued in 2006. Pet. 11-12, 15, 27-30. Even assuming that Wyeth were correct that the FDA's preamble supports its position regarding preemption and that the preamble filled a statutory gap or clarified a statutory ambiguity entitling it to judicial deference – both positions with which we disagree – any federal legal command created by the preamble could not have had legal effect until 2006, years after the approval of the Phenergan label.

Finally, there is good reason why no appellate court has ever embraced Wyeth's position. The Food, Drug, and Cosmetic Act (FDCA) bars preemption unless there is a "direct and positive conflict" between federal and state law. Pub. L.

87-781, § 202, 76 Stat. 780, 793 (1962). Moreover, FDA regulations provide that FDA-approved drug "labeling *shall* be revised to include a warning as soon as there is reasonable evidence of an association of a serious hazard with a drug," 21 C.F.R. § 201.80(e) (emphasis added), and affirmatively permit manufacturers, without prior FDA approval, to amend labels to "add or strengthen an instruction about dosage and administration that is intended to increase the safe use of the drug product." 21 C.F.R. § 314.70(c)(6)(iii)(C). Thus, the circumstances under which FDA regulation could conflict with a state-law damages action are very narrow, if not non-existent. Review should be denied for that reason as well, particularly in the absence of a division among the appellate courts.

STATEMENT OF THE CASE

A. Factual Background

On April 7, 2000, Diana Levine received injections of Wyeth's prescription drug Phenergan to treat nausea associated with a migraine headache. The drug was first administered by intramuscular injection. Pet. App. 2a. Later that day, the drug was administered intravenously through a technique known as direct IV, or "IV push." *Id.* In this method, a syringe pushes medication directly into the patient's vein. The method is called "direct" to distinguish it from a more common means of intravenous administration in which the medication is placed into a stream of saline flowing from a hanging IV bag. Tr. vol. I, at 194. Wyeth has known for decades that when Phenergan is administered by the IV push method, even by experienced clinicians, inadvertent arterial contact can result. *Id.* at 218-24; *see also id.* at 216 (referring to at least 20 reported cases "where Phenergan has caused an amputation," all resulting from IV push). Based on undisputed expert testimony, the trial court found as fact that

> [o]ne way to reduce the risk of inadvertent intra-arterial injection is to set up a free-flowing IV bag and introduce the drug into the IV solution. This is an alternative to injection through the [IV push] infusion set into a patient's vein. Administration through a free-flowing IV bag reduces the risk of inadvertent arterial injection because the nurse or physician can be more certain that the needle has been placed in a vein. A solution dripping from an IV bag will not flow freely into an artery due to back pressure from the patient.

Pet. App. 52a-53a (fact #4, citing Tr. vol. I, at 194-98, 208-14); *see also, e.g.*, Tr. vol. I, at 195-97 (Dr. Harold Green) (explaining that use of hanging IV involves virtually no risk of arterial exposure and is "far safer" than IV push).

Wyeth has also known that when Phenergan comes in contact with an artery, the artery dies, and necrosis, gangrene, and amputation result. Four experts testified that if Phenergan is used intravenously, it should be done only through a hanging IV bag and that the label should have precluded use of IV push. *Id.* vol. I, at 230-33; vol. II, at 28, 73-74, 97-98, 111. One of Wyeth's experts acknowledged that he would hesitate to use direct IV injection for use in non-life-threatening situations and, at his deposition, stated that he would have written the label to instruct that Phenergan be administered into a running, established IV. *Id.* vol. IV, at 168-69. Another Wyeth expert agreed with Ms. Levine's expert that it was safer to administer Phenergan through a free-flowing IV than through the direct method. *See* Pet. App. 55a (fact #13). On Phenergan's label, however, use of the IV push method is not foreclosed, contraindicated, or even mentioned. And, as the Vermont Supreme Court held, the FDA never considered any warning

regarding the safety (or lack thereof) of the IV push method. *Id.* at 16a-19a.[1]

Because the IV push method was used to administer Phenergan to Ms. Levine, the drug penetrated her artery. Pet. App. 2a. For seven weeks after the injection, Ms. Levine suffered unimaginable physical and emotional pain as she watched her right hand turn black and die. *Id.*; Tr. vol. III, at 38 (Dr. Mark Bucksbaum) ("Pain scales usually are run from one to ten. This is a ten. ... there's not much worse than this type of scenario."), at 165-66 (Ms. Levine describing excruciating pain, terror, and fear of dying and losing her arm). In short, as a result of being subjected to an unsafe and unnecessary method of administration of a drug to curb nausea, Ms. Levine endured two amputations. She first lost her right hand and then her right arm up to the elbow, which forever destroyed her ability to play music – her profession and lifelong passion.

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[1]Without citing any authority, let alone any FDA findings, the petition (at 8 & n.3) lauds the efficacy of IV push for its alleged speed of administration and ability to combat nausea and dehydration, suggesting that the FDA sanctioned the IV push method for these reasons. No record evidence supports that suggestion. The evidence at trial demonstrated that although IV administration may provide somewhat faster relief from nausea, that small benefit does not warrant the risk of *IV push* administration. *See, e.g.*, Tr. vol. I, at 184 (Dr. John Mathew) ("the enormous risk – even though the odds might be small in any one instance – is nowhere near offset by the small gain of 15 to 20 minutes less vomiting or nausea."); vol. II, at 81-82 (Jessica Fisch, P.A.) ("It can work faster, but that's not an excuse for taking somebody's arm and having some kind of extravasation injury that means they lose their fingers or their arm. It's nausea. It's not – this isn't – a heart attack, this is somebody who's sick to their stomach."). The notion that an *IV push* administration of *Phenergan* was necessary to prevent dehydration is also at odds with the record. The evidence showed that vomiting emergency room patients are hydrated by administering a dripping IV containing a solution that may or may not include a drug to counteract the vomiting. *See* Tr. vol. I, at 197-98 (Dr. Harold Green).

B. The FDA Drug Approval Process, The FDCA's Relationship With State Law, And Approval Of The Phenergan Label.

1. FDA Approval And Drug Labeling

Since enactment of the FDCA in 1938, new prescription drugs must be approved by the FDA before they are marketed. From 1938 to 1962, new drugs were approved after an FDA review regarding the drug's safety. Since 1962, drugs are reviewed for efficacy as well, which, as Wyeth put it below, "enabl[ed] FDA to balance risks against benefits." Br. for Defendant-Appellant, at 11, in *Levine v. Wyeth*, No. 2004-384 (Vt. S. Ct. filed Jan. 19, 2004). As the Vermont Supreme Court explained, a manufacturer seeking to market a prescription drug must file a new drug application (NDA) with the FDA. Pet. App. 9a (citing 21 U.S.C. § 355(a)). The agency must approve the NDA "unless it fails to meet certain criteria, including whether test results and other information establish that the drug is 'safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof,' whether there is 'substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling thereof,' and whether, 'based on a fair evaluation of all material facts, such labeling is false or misleading in any particular.'" *Id.* (quoting 21 U.S.C. § 355(d)).

Because prescription drug labeling provides information used by clinicians to prescribe and administer an approved drug, the FDA's regulations describe in detail the proper form and content for labeling. *See generally* 21 C.F.R. Part 201. Once a drug is approved by the agency, it generally must be accompanied by labeling in the form approved by the FDA. *See* 21 C.F.R. § 314.70(b)(2)(v). The label's content is not, however, set in stone. Rather, a manufacturer is *required* to

alter its labeling in certain circumstances. FDA regulations provide that approved drug "labeling *shall* be revised to include a warning as soon as there is reasonable evidence of an association of a serious hazard with a drug[.]" *Id.* § 201.80(e) (emphasis added). Moreover, the FDA is not required to approve all label changes before drug manufacturers make them. Manufacturers are permitted to revise labels, without prior FDA approval, to

> add or strengthen a contraindication, warning, precaution, or adverse reaction; [and to] add or strengthen an instruction about dosage and administration that is intended to increase the safe use of the drug product[.]

Id. § 314.70(c)(6)(iii)(A), (C); *see also* 44 Fed. Reg. 37434, 37447 (1979) (noting that revised warnings may be made by various means, including via label changes and "Dear Doctor" letters).

2. The Relationship Between Federal Drug Regulation And State Law

Throughout the nearly 70 years since enactment of the FDCA, the states' traditional common-law tort systems have compensated injured persons for injuries caused by prescription drugs. As enacted in 1938, the FDCA was silent regarding its effect on state law and did not suggest that state-law damages claims of any kind would be preempted; indeed, "Congress rejected a provision in a draft of the original FD&C Act providing a federal cause of action for damages [for injuries caused by prescription drugs] because 'a common law right of action [already] exists.'" Robert Adler & Richard Mann, *Preemption and Medical Devices: The Courts Run Amok*, 59 Mo. L. Rev. 895, 924 & n.130 (1995). Thereafter, when enacting the 1962 FDCA requirements regarding drug efficacy,

Congress included the following provision regarding preemption:

> Nothing in the amendments made by this Act to the federal Food, Drug, and Cosmetic Act shall be construed as invalidating any provision of State law which would be valid in the absence of such amendments unless there is a direct and positive conflict between such amendments and such provision of State law.

Pub. L. No. 87-781, § 202.

Until recently, the FDA had never suggested that state-law products liability suits constituted such "a direct and positive conflict." To the contrary, on at least two occasions, the FDA took the opposite view. In 1979 and 1998, in preambles accompanying drug regulations, the agency stated that state tort law did not interfere with federal regulation. *See* 63 Fed. Reg. 66378, 66384 (1998) (regulation addressing Medication Guides, issued pursuant to FDA's authority over drug labeling) ("FDA does not believe that the evolution of state tort law will cause the development of standards that would be at odds with the agency's regulations."); 44 Fed. Reg. at 37437 ("It is not the intent of the FDA to influence the civil tort liability of the manufacturer.").

In December 2000, the FDA proposed a new regulation to address the form and content of drug labeling, the principal purpose of which was to require a new "Highlights" section on drug labels. At that time, the agency noted that "this proposed rule does not preempt State law." 65 Fed. Reg. 81082, 81103 (2000). In 2006, in finalizing these labeling rules, the agency took a different view, claiming in the regulatory preamble that, in narrow circumstances, the FDA's approval of a drug's labeling may preempt a state tort claim based on a failure to warn. The agency stated that

> FDA believes that State laws conflict with and stand as an obstacle to achievement of the full objectives and purposes of Federal law when they purport to compel a firm to include in labeling or advertising a statement that FDA has considered and found scientifically unsubstantiated . . . [or when State law] purports to preclude a firm from including in labeling or advertising a statement that is included in prescription drug labeling.

71 Fed. Reg. 3922, 3935 (2006), Pet. App. 136a.

3. History Of The Phenergan Label

The drug approval process necessarily involves some back-and-forth between the drug manufacturer and the FDA, as the manufacturer submits proposed labeling with its NDA and the FDA must respond. Phenergan and its labeling were first approved by the FDA in 1955, before the agency had authority over drug efficacy. Although the petition paints a history of intense interaction between Wyeth and the FDA regarding the labeling for Phenergan, it was nothing of the sort. In the more than 50 years since Phenergan's approval, the record reveals only two related sets of interactions between the FDA and Wyeth regarding the Phenergan label. Both were apparently triggered by Wyeth's 1981 submission of a supplemental NDA in response to an agency-wide effort to revise drug labeling. *See* Pet. 7. The first interaction culminated in 1987 with a revised warning concerning the already-known and undisputed adverse effects of inadvertent arterial exposure to Phenergan. Pet. App. 150a-157a. This interaction between Wyeth and the FDA did not concern the method of administration of Phenergan in general, or the IV push method in particular. *See id.*

Second, as part of the FDA's review, Wyeth was required to submit proposed labeling for Phenergan, which

necessarily included all of the topics reflected in the original label, including warnings about inadvertent arterial exposure. As part of that submission, Wyeth proposed wording for the instruction concerning administration of Phenergan through a hanging IV bag that was somewhat different from the label in current use. Neither version concerned the IV push method. *See* Pet. App. 4a-5a n.1 (comparing current label with proposal). In a 1997 letter, issued some 16 years after Wyeth's original submission, the FDA, without any explanation, directed Wyeth to "retain [the] verbiage in [the] current label" with regard to inadvertent arterial exposure. Pet. App. 162a. *Id.*

In sum, none of the exchanges between Wyeth and the FDA even mentions the IV push method of administration, and Wyeth presented no evidence at trial that it or the FDA ever considered amending the Phenergan label to address the safety or efficacy of the IV push method.

C. The Proceedings Below

Ms. Levine brought suit against Wyeth in Vermont Superior Court to recover compensation for her life-altering injuries. As noted earlier, at trial, medical experts testified that Wyeth should have precluded use of the IV push method because of its potentially devastating consequences. The jury found Wyeth liable for failing to warn clinicians not to use that method and awarded compensation to Ms. Levine for her economic and non-economic losses. The trial court denied Wyeth's motion for judgment in its favor on federal preemption grounds, both at the close of evidence and post-verdict. Pet. App. 49a.

The Vermont Supreme Court affirmed, holding that Ms. Levine's claims are not preempted by the federal law. The court began by noting Wyeth's acknowledgment that the FDCA does not expressly preempt state law nor occupy the field of prescription drug regulation, and thus focused its analysis on

Wyeth's contention that Ms. Levine's recovery was impliedly preempted because it "actually conflicts with federal law." Pet. App. 8a (quoting *Cipollone v. Liggett Group, Inc.*, 505 U.S. 504, 516 (1992)).[2]

The Vermont Supreme Court then explained that in light of 21 C.F.R. § 314.70(c)(6)(iii) – the regulation that permits manufacturers to add or strengthen a contraindication or warning, or add or strengthen an instruction about dosage and administration, without FDA approval – there is no general "conflict between federal labeling requirements and state failure-to-warn claims." Pet. App. 11a. As the court put it: "Section 314.70(c) allows, and arguably encourages, manufacturers to add and strengthen warnings that, despite FDA approval, are insufficient to protect consumers. State tort claims simply give these manufacturers a concrete incentive to take this action as quickly as possible." *Id.*

The court then rejected Wyeth's assertion that the FDA's actions with respect to the Phenergan label preempted Ms. Levine's claims on the ground that Wyeth's position lacked any support in the factual record. The court found no evidence that the FDA considered the safety (or lack thereof) of the IV push method of administration. *See generally id.* at 16a-19a; *see also, e.g., id.* at 17a ("Neither the letters [exchanged

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[2]At oral argument, Wyeth's counsel emphasized that its claim of conflict preemption was quite narrow and turned solely on what Wyeth maintained were facts peculiar to this case:

> I want to emphasize to the Court that the issue as presented here is very narrow and very particularized. . . . It's focused on Phenergan in the facts of this case. Wyeth is not contending for field preemption, for the ouster of Vermont law, tort law [is] not at issue here . . . nor are we arguing that the mere compliance with federal labeling requirements in and of itself creates a conflict preemption.

Vermont S. Ct. Oral Arg. Tr. at 7 (Oct. 5, 2007).

between FDA and Wyeth] nor any other evidence presented to the jury indicated that the FDA wished to preserve the use of IV push as a method of administering Phenergan."); 19a ("There is no evidence that the FDA intended to prohibit defendant from strengthening the Phenergan label [with an instruction precluding IV push] pursuant to § 314.70(c)."). For the same reason, the court also rejected Wyeth's contention that the FDA's 1987 direction to "retain verbiage in current label" was tantamount to rejecting a warning about the IV push method. *Id.* at 17a-18a. The notion that this cryptic statement precluded a warning about IV push was, the court said, "an unsupported hypothesis" because "the rejected [Wyeth] proposal would not have eliminated IV push as an option for administering Phenergan." *Id.* at 18a; *see id.* at 4a-5a n.1 (Wyeth's proposal).

Finally, the court dismissed Wyeth's claim for deference to the FDA's 2006 regulatory preamble, which asserts that, in limited circumstances, state failure-to-warn claims are preempted by the FDA's approval of drug labeling. *Id.* at 24a. Declining to address Ms. Levine's claim that the 2006 preamble was ineffective because it was promulgated without the requisite notice and comment, *id.* at 25a, the court held that the preamble was neither entitled to *Chevron* deference nor had the "power to persuade" under *Skidmore v. Swift & Co.*, 323 U.S. 134, 140 (1944)). *See id.* at 25a-26a. The agency's claim of conflict with federal law, the Vermont Supreme Court held, did not warrant deference because it was flatly at odds with both the FDA's regulation permitting manufacturers "to add or strengthen a warning 'to increase the safe use of the drug product' without prior FDA approval," Pet. App. 26a (quoting 21 C.F.R. § 314.70(c)(6)(iii)(C)), and with Congress's express directive that state law concerning prescription drugs be superseded only when it poses a "'direct and positive conflict' with federal law." *Id.* (quoting 76 Stat. 793).

REASONS FOR DENYING THE WRIT

A. There Is No Division In Appellate Authority On The Question Presented.

No appellate court – federal or state – has ever held that the FDA's drug approval authority or its authority over drug labeling preempts a state-law tort suit, whether premised on the manufacturer's failure to warn or on any other ground. To the contrary, every appellate court to have addressed the issue has ruled that FDA approval or compliance with FDA regulations does not preempt any state-law damage claims. *See, e.g., Tobin v. Astra Pharm. Prods., Inc.*, 993 F.2d 528, 537 (6th Cir.), *cert. denied*, 510 U.S. 914 (1993); *Osburn v. Anchor Labs.*, 825 F.2d 908, 911-13 (5th Cir. 1987), *cert. denied*, 485 U.S. 1009 (1988); *Wells v. Ortho Pharm. Corp.*, 788 F.2d 741, 746 (11th Cir.); *cert. denied*, 479 U.S. 950 (1986); *Feldman v. Lederle Labs.*, 592 A.2d 1176, 1185-97 (N.J. 1991), *cert. denied*, 505 U.S. 1219 (1992); *Kurer v. Parke, Davis & Co.*, 679 N.W.2d 867, 875 (Wis. App. 2004) ("As numerous courts have concluded, FDA regulations do not preempt the imposition of state common law liability for failure to warn claims.") (citations omitted). Thus, there is no conflict in appellate authority and, for that reason alone, no justification for this Court's intervention.[3]

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[3]In addition to the unanimity among appellate courts, the great majority of trial courts to have addressed the question have come to the same conclusion. *See, e.g., Jackson v. Pfizer, Inc.*, 432 F. Supp. 2d 964 (D. Neb. 2006); *Laisure-Radke v. Par Pharm., Inc.*, 426 F. Supp. 2d 1163, 1169 (W.D. Wash. 2006); *Peters v. Astrazeneca, LP*, 417 F. Supp. 2d 1051, 1054-57 (W.D. Wis. 2006); *Witczak v. Pfizer, Inc.*, 377 F. Supp. 2d 726, 728-32 (D. Minn. 2005); *Cartwright v. Pfizer, Inc.*, 369 F. Supp. 2d 876, 881-87 (E.D. Tex. 2005); *McNellis v. Pfizer, Inc.*, 2005 WL 3752269 (D.N.J. Dec. 29, 2005); *Zikis v. Pfizer, Inc.*, 2005 WL 1126909 (N.D. Ill. May 9, 2005);

(continued...)

B. Wyeth Seeks Review On A Question Not Presented By This Case.

The question presented by Wyeth is whether the "labeling judgments" made by the FDA regarding a drug's safety and efficacy preempt state-law product liability claims premised on "differing label judgments." Pet. i. This case does not present that question because the Vermont Supreme Court correctly found, as a matter of fact, that Ms. Levine's recovery

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[3](...continued)

Motus v. Pfizer, Inc., 127 F. Supp. 2d 1085, 1091-1100 (C.D. Cal. 2000), *aff'g dismissal on other grounds*, 358 F.3d 659 (9th Cir. 2004); *In re Paxil Litig.*, 2002WL 31375497, *1 (C.D. Cal. Oct. 18, 2002); *Eve Sandoz Pharm. Corp.*, 2002 WL 181972 (S.D. Ind. Jan. 28, 2002); *Caraker v. Sandoz Pharm. Corp.*, 172 F. Supp. 2d 1018, 1029-44 (S.D. Ill. 2001); *Globetti v. Sandoz Pharm. Corp.*, 2001 WL 419160 (N.D. Ala. Mar. 5, 2001); *Mazur v. Merck & Co.*, 742 F. Supp. 239, 245-48 (E.D. Pa. 1990); *Kociemba v. Searle & Co.*, 680 F. Supp. 1293, 1298-1300 (D. Minn. 1988); *Graham v. Wyeth Labs.*, 666 F. Supp. 1483, 1488-93 (D. Kan. 1987);*Stephens v. G.D. Searle*, 602 F. Supp. 379, 382 (E.D. Mich. 1985).

The prevailing view that the FDCA does not preempt state-law failure-to-warn claims is consistent with the entrenched common-law rule that compliance with federal statutes and regulations may be considered by the finder of fact in determining a manufacturer's liability, but is not a complete defense to a products liability claim. *Restatement of Torts (Third) – Products Liability* § 4(b) (Am. Law Inst. 1988); *see, e.g., McEwen v. Ortho Pharm. Corp.*, 528 P.2d 522, 534 (Or. 1974) (citing cases); *Stevens v. Parke, Davis & Co.*, 507 P.2d 653, 661 (Cal. 1973). The jury in this case was instructed accordingly, without objection from Wyeth. *See* Jury Instructions, Printed Case, vol. II, at 348 ("You may consider evidence of compliance by Wyeth with FDA requirements in obtaining approval for the Phenergan warning. Compliance with FDA requirements does not by itself establish that the warning was adequate for purposes of this case. You must decide whether the instructions and warnings were adequate based upon all the evidence presented in this trial including evidence about the FDA process.").

was *not* based on a labeling judgment different from a labeling judgment made by the FDA.

1. Wyeth has phrased the question presented to try to take advantage of the scant trial court authority that holds that, in narrow circumstances, certain state-law failure-to-warn claims are preempted by the FDA's specific regulatory judgments regarding a particular prescription drug label. For instance, in *Needleman v. Pfizer Inc.*, 2004 WL 1773697 (N.D. Tex. Aug. 6, 2004), the plaintiff claimed that the manufacturer of the anti-depression drug Zoloft, one of a family of drugs known as SSRIs, had failed adequately to warn of Zoloft's association with certain side-effects that led to the plaintiff's husband's suicide. The court found the plaintiff's claim preempted, but only because of the highly unusual and intensive post-marketing FDA reevaluation of SSRI labeling. As the court put it: "[T]he FDA conducted reviews of the issue in 1991, 1992, 1997, and 2002, each time finding no scientific basis for a warning that SSRIs cause suicide. The government concluded that any warning suggesting a link between SSRIs and suicide would be false, misleading, contrary to the public interest, and should not be given." *Id.* at *2. The court thus concluded that "Plaintiffs' state law failure to warn claim is preempted by the FDCA and the FDA's rulings on the warnings required for Zoloft." *Id.* at *5.

The other district court cases cited by Wyeth generally fall into the same category; they find preemption where the failure to warn upon which the plaintiff's damages claim was premised was found to be at odds with specific findings made by the FDA on the exact same topic. *See Colacicco v. Apotex, Inc.*, 432 F. Supp. 2d 514 (E.D. Pa. 2006) (finding preemption in an SSRI case); *In re Bextra & Celebrex Marketing Sales Practices and Prod. Liab. Litig.*, 2006 WL 2374742 (N.D. Cal. 2006) (finding preemption of one claim premised on an

"attempt to require Pfizer to include in its Celebrex promotion a warning which the FDA has considered and found to be scientifically unsubstantiated," but rejecting preemption of another claim where FDA had made no similar finding).[4]

In our judgment, the district court decisions on which Wyeth relies are incorrect because, among other reasons, they fail to give sufficient weight to Congress's narrow understanding of preemption under the FDCA and the governing FDA regulations under which manufacturers may amend drug labels to strengthen warnings, contraindications, and instructions to protect patient health and safety. For present purposes, however, these cases are important because of their narrow scope, and the distinction that they draw between situations in which the FDA has made a specific determination contrary to the state-law warning that underlies the plaintiff's claim, on the one hand, and run-of-the-mill failure-to-warn cases such as Ms. Levine's, on the other. *See In re Bextra*, 2006 WL 2374742, at *10 (contrasting a case involving "a warning which the FDA has considered and found to be

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[4]The other district court case cited by Wyeth, *Ehlis v. Shire Richwood, Inc.*, 233 F. Supp. 2d 1189 (D.N.D. 2002), found preemption of a state-law claim in an alternative holding that contained no analysis of the degree of FDA involvement over the drug label in question and relied almost exclusively on precedent regarding the *express preemption* provision of the federal medical device law. *See id.* at 1197-98. Wyeth (at 17) suggests that *Ehlis* was affirmed on preemption grounds, but, in fact, it was affirmed solely on state-law grounds wholly unrelated to preemption. *See Ehlis v. Shire Richwood, Inc.*, 367 F.3d 1013 (8th Cir. 2004). Like *Ehlis*, *Horn v. Thoratec Corp.*, 376 F.3d 163 (3d Cir. 2004), cited in the petition at 21 and 29, is inapposite because it construed the medical device law's express preemption provision. *See* Pet. App. 14a ("In Horn, the Third Circuit relied on an express preemption clause in the FDCA that relates only to medical devices. . . . Because no such clause exists for prescription drugs, Horn's reasoning does not apply to this case.").

scientifically unsubstantiated" with "a case where the FDA has not considered the risks of which plaintiffs claim the drug manufacturer should have warned[.]") The Vermont Supreme Court drew the very same distinction, contrasting Ms. Levine's case with *Needleman*, where the finding of preemption was based "on the facts of the *Zoloft* litigation" and the FDA's specific rejection of "the warning advocated by the plaintiff." Pet. App. 13a.

This case is at the other end of the spectrum from a case like *Needleman*. As discussed above (at 9-10, 12), no record evidence suggests that the FDA even considered the particular safety ramifications of the IV push method for Phenergan administration, let alone specifically rejected a warning that would have precluded or limited its use. *See, e.g., id.* at 17a (finding no support for Wyeth's speculation that the FDA believed "it would have harmed patients [to] eliminat[e] IV push as an option for administering Phenergan"), 19a (finding "no evidence" that FDA wanted to preserve IV push or to preclude a warning against it). As the Vermont Supreme Court explained, Wyeth "has provided a number of letters exchanged by the FDA and defendant regarding Phenergan's label, but these letters do not indicate the FDA's opinion of the value of IV-push administration." *Id.* at 17a. Thus, as this case comes to this Court, it does not implicate the question presented or the small minority of district court rulings that find preemption of state-law duty-to-warn claims based on specific FDA labeling judgments concerning particular prescription drug labels.[5]

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[5]The letters referred to by the Vermont Supreme Court are included in the appendix to the Petition. They do not mention, let alone discuss, the safety or efficacy of the IV push method. Wyeth's suggestion (at 6-9) that the FDA affirmatively sanctioned use of the IV push method is simply wrong. The label warnings cited by Wyeth concern the undisputed risks of

(continued...)

2. For much the same reasons, the petition also does not present any genuine issue regarding the applicability of the 2006 FDA regulatory preamble on which Wyeth relies. The petition fails to describe the preamble's operative legal standard under which, in the FDA's view, the agency's labeling approval will preempt a state-law claim premised on a failure to warn. That legal standard – which includes two bases for preemption – warrants a full quotation:

> FDA believes that State laws conflict with and stand as an obstacle to achievement of the full objectives and purposes of Federal law when they purport to compel a firm to include in labeling or advertising a statement that FDA has considered and found scientifically unsubstantiated. In such cases, including the statement in labeling or advertising would render the drug misbranded under the act (21 U.S.C. 352(a) and (f)). The agency believes that State law conflicts with and stands as an obstacle to achievement of the full objectives and purposes of Federal law if it purports to preclude a firm from including in labeling or advertising a statement that is included in prescription drug labeling. By complying with the State law in such a case and removing the statement from labeling, the firm would be omitting a statement required under § 201.100(c)(1) as a condition on the exemption from the

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[5](...continued)
arterial exposure to Phenergan and the IV drip method of administration, that is, administration through a hanging IV bag, not the IV push method. The petition's statement that "[b]etween 1967 and 1981, FDA worked closely with Wyeth through a series of communications and at least one in-person meeting to refine Phenergan's warnings with respect to IV push administration[,]" Pet. 6-7, has no basis in the record and, not surprisingly, is not accompanied by *any* citation.

> requirement of adequate directions for use, and the omission would misbrand the drug under 21 U.S.C. 352(f)(1). The drug might also be misbranded on the ground that the omission is material within the meaning of 21 U.S.C. 321(n) and makes the labeling or advertising misleading under 21 U.S.C. 352(a) or (n).

71 Fed. Reg. at 3935, Pet. App. 136a.[6]

After setting out the foregoing legal standard, the preamble provides six examples of state-law claims that the FDA believes would give rise to preemption, only two of which even arguably bear on Wyeth's claim for preemption here: "claims that a drug sponsor breached an obligation to warn by failing to include a statement in labeling or advertising, the substance of which had been proposed to FDA for inclusion in labeling, if that statement was not required by FDA at the time

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[6]Wyeth erroneously claims support for its expansive view of the preamble in recent FDA amicus briefs but ignores their key passages. For instance, the agency's amicus brief in *Perry v. Novartis Pharmaceuticals*, Civ. No. 05-5350 (E.D. Pa.) (filed Sept. 22, 2006) (hereafter "*Perry* Br."), cited in the petition at 28, references as the operative legal principle the exact portion of the preamble quoted above. *Perry* Br. 10. The FDA brief also explains:

> A failure-to-warn claim is not preempted merely because it imposes liability for a manufacturer's failure to provide a warning that has not yet been required by FDA. Federal regulations explicitly recognize that manufacturers can, and in some limited instances must, modify their labels to add new warnings of hazards associated with the drug without awaiting prior FDA approval. *See* 21 C.F.R. § 314.70(c)(7); 21 C.F.R. § 201.56. [Although the FDA may ultimately reject such a labeling change,] "[t]o the extent, therefore, that the defendants argue that federal preemption bars *any* failure-to-warn claim premised on a drug manufacturer's failure to provide a warning not contained in the drug's approved labeling, the defendants are incorrect."

Id. at 10-11.

plaintiff claims the sponsor had an obligation to warn"; and "claims that a drug sponsor breached an obligation to warn by failing to include in labeling or in advertising a statement the substance of which FDA has prohibited in labeling or advertising[.]" *Id.* at 3936, Pet. App. 138a-139a.

The foregoing discussion of the factual record, and the Vermont's Supreme Court's findings based on it, demonstrate that Ms. Levine's claims did not "purport to compel [Wyeth] to include in "labeling or advertising a statement that FDA ha[d] considered and found scientifically unsubstantiated." Nor did they "purport[] to preclude [Wyeth] from including in labeling or advertising a statement that is included in prescription drug labeling." As explained above, there is no evidence that the FDA considered a statement that would have precluded the use of IV push, let alone found it scientifically unsubstantiated, and no one has suggested that Ms. Levine sought to preclude a statement that was on the approved label. Her claim is that Wyeth should have included an instruction that would have foreclosed use of the IV push method for administering Phenergan.

The irrelevance of the 2006 preamble to this case thus underscores the conclusion that, *as it comes to this Court,* this case does not genuinely implicate the question presented, and it would not do so unless this Court were first to overturn the Vermont courts' factual findings. The petition tacitly understands this problem and thus spills considerable ink attempting to show that the FDA considered and rejected an instruction precluding the IV push method and made a conscious, affirmative decision to retain that method for administering Phenergan. Pet. 6-9. The difficulty with making that argument below, as the Vermont Supreme Court found, was that it has no basis in the factual record. That difficulty is compounded at this juncture because, except in extraordinary

circumstances, this Court does not grant review "when the asserted error consists of erroneous factual findings." S. Ct. Rule 10. For this reason as well, review should be denied.

C. This Case Is An Inappropriate Vehicle For Deciding Whether The FDA's 2006 Regulatory Preamble Is Entitled To Deference Because The Preamble Post-Dates The FDA's Purportedly Preemptive Labeling Decisions Regarding Phenergan.

The petition argues that the courts must defer to the FDA's views on preemption as set forth in the agency's 2006 preamble. Pet. 27-30. As explained in the previous section, Ms. Levine's recovery would not be preempted under the express terms of the preamble. Moreover, the FDA's views on preemption of state-law damages claims have never been the subject of *any* appellate decision. Indeed, only one appellate court has even mentioned those views, and, in that case, the Second Circuit suggested in dicta that deference would be unwarranted because "an agency cannot supply, on Congress's behalf, the clear legislative statement of intent required to overcome the presumption against preemption." *Desiano v. Warner-Lambert & Co.*, 467 F.3d 85, 97 n.9 (2d Cir. 2006) (quoting *Alexander v. Sandoval*, 532 U.S. 275, 291 (2001) ("Agencies may play the sorcerer's apprentice but not the sorcerer himself.")).

Even if the Court were inclined, absent any appellate authority on the topic, to consider whether the 2006 preamble is entitled to deference, this case is not an appropriate vehicle for doing so because deference may not be accorded retroactively, that is, in a situation where the FDA labeling decisions said to have preemptive effect pre-date the FDA's views for which deference is claimed. An agency's legislative rule promulgated pursuant to a proper congressional grant of authority, like a congressional statute, will not have retroactive

effect unless the rule's text demands it and the congressional delegation includes the authority to issue retroactive rules. *Bowen v. Georgetown Univ. Hosp.*, 488 U.S. 204, 208-09 (1988). That is so because regulations that are properly authorized by Congress, like congressional statutes themselves, have the effect of law. The same principle applies in a situation where, as Wyeth asserts here, the agency's views expressed in a format other than an agency regulation are claimed to have the force of law. *See* Pet. 29-30.

In our view, Congress has not delegated to the FDA the authority to patrol the borderline between federal regulatory power and state tort law, and, even if it had, deference to the 2006 preamble would be unwarranted for a host of reasons. *See infra* at 26-29. But assuming that this Court were inclined to consider whether the 2006 preamble is entitled to deference, it should do so only in a case where, at the relevant time, the federal legal command said to have preemptive effect – the 2006 preamble – arguably could have been in conflict with the state law said to be preempted.

But that is impossible here. According to Wyeth, the most recent relevant labeling decision regarding Phenergan was made in September 1998. *See* Pet. 8 (referring to FDA letter reproduced at Pet. App. 164a). In *1998*, federal law regarding the preemptive effect of FDA approval of drug labeling could not have included the *2006* preamble. One commentator has made this point in the context of the SSRI litigation, in which, as in Ms. Levine's case, the agency's decisions regarding the product label pre-dated the agency's view that certain tort claims are preempted: "The FDA henceforth might characterize as misbranding any [future] labeling change that the FDA itself declines to require. . . . [W]hat the FDA cannot do – with or without *Chevron* deference – is to impose that characterization upon past events where the legal landscape offered only a

glimmer, at best, of such a view. The prerogative of filling gaps and resolving ambiguities in statutes does not embrace the rewriting of history." Richard Nagareda, *FDA Preemption: When Tort Law Meets The Administrative State*, 1 J. Tort Law iss.1, art. 4, at 35 (2006), available at www.bepress.com/jtl/vol1/iss1/art4/; *see also* Pet. App. 26a (noting retroactivity problem).[7]

In sum, if and when this Court wishes to consider whether and in what circumstances the FDA's drug labeling authority preempts state-law failure-to-warn claims, including the legal effect, if any, of the FDA's views on those questions, it should do so in a case, unlike this one, where the relevant FDA labeling judgments post-date the agency statements for which deference is claimed.[8]

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[7]The agency is entitled to its opinion on the preemptive effect of the FDCA on state-law tort claims – that is, without treating the 2006 preamble as part of the body of substantive federal law – but it is entitled to no deference on that "pure question of statutory construction," *INS v. Cardoza-Fonseca*, 480 U.S. 421, 446 (1987), or, at best, only to the weight attributable to the preamble's persuasive force. *See Skidmore v. Swift & Co.*, 323 U.S. 134, 140 (1944). Wyeth, however, seeks substantial deference to the 2006 preamble of the kind that flows from an agency's proper exercise of its delegated law-making authority. *See* Pet. 29 (claiming "FDA's substantive interpretation of its own regulations should be entitled to considerable deference"); *see also In re Bextra*, 2006 WL 2374742, at *6-*7 (according *Chevron*-type deference to 2006 preamble). That purported addition to federal law can only be applied prospectively.

[8]This case is a poor vehicle for considering the question presented for the related reason that the Phenergan labeling was originally approved in 1955 before any efficacy review and thus without any risk-benefit analysis. Although the label went through some subsequent FDA review and revision, the situation presented by this case raises the question whether the drug's serious risks were searchingly weighed against its benefits when used

(continued...)

D. Wyeth Is Wrong On The Merits.

As discussed above, there is no basis for the Court to look past its ordinary, time-honored restraints on review. Moreover, the Vermont Supreme Court resolved the merits correctly.

1. The parties agree that the FDCA does not expressly preempt state-law damages claims or occupy the field of prescription drug regulation. Thus, the question here is whether Ms. Levine's state-law claim is impliedly preempted because it actually conflicts with federal law, that is, whether her recovery renders Wyeth's compliance with state and federal law physically impossible or whether Wyeth's compliance with state law would erect an impermissible obstacle to the accomplishment of federal objectives.[9]

As the Vermont Supreme Court held, it would not have been impossible to comply with a state-law duty to warn against IV push and federal labeling requirements because those requirements expressly give manufacturers the right to revise labels to include contraindications, warnings, and instructions that enhance patient safety without prior FDA approval. 21 C.F.R. § 314.70(c)(6)(iii)(A), (C). And FDA regulations say that "labeling *shall* be revised to include a warning as soon as

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[8](...continued)
to combat a non-life threatening common malady such as nausea. *See* Tr. vol. I, at 236, 249-50 (discussing ramifications of fact that FDA did not conduct risk-benefit analysis at time Phenergan was approved).

[9]Wyeth's attempt to turn the Vermont Supreme Court's brief mention of the presumption against preemption into a basis for review is meritless. The presumption is based on a long, unbroken line of authority from this Court, including many cases involving claims that federal regulatory schemes preempt state tort law. It applies with full force here. *See* Pet. App. 7a (citing cases).

there is reasonable evidence of an association of a serious hazard with a drug." 21 C.F.R. § 201.80(e) (emphasis added). Based on these regulations, the FDA itself has stated that a "failure-to-warn claim is not preempted merely because it imposes liability for a manufacturer's failure to provide a warning that has not yet been required by FDA." *Perry* Br. 11.

Moreover, it is not physically impossible for Wyeth to comply with federal requirements and the state court's damages verdict, which does not require Wyeth to alter its conduct but only to pay damages to Ms. Levine. As the Court recently explained in *Bates v. Dow Agrosciences LLC*, a "requirement is a rule of law that must be obeyed; an event, such as a jury verdict, that merely motivates an optional decision [to re-label the product] is not a requirement." 544 U.S. 431, 443 (2005).[10]

Ms. Levine's recovery likewise poses no obstacle to the accomplishment of federal objectives. Wyeth claims that the Vermont Supreme Court's decision regarding obstacle preemption is at odds with this Court's view that federal "savings clauses" do not bar the application of ordinary conflict preemption principles. Pet. 23. The Vermont court did not eschew those principles. Rather, it correctly held that, because the FDCA limits preemption to "direct and positive conflict[s]" between state and federal law, Pub. L. 87-781, § 202, there can be no obstacle to federal objectives where a manufacturer is able to comply with applicable state and federal duties. *See* Pet. App. 21a-23a. In any event, as explained above, the FDA never considered and found scientifically unsubstantiated a warning foreclosing or limiting the IV push method for administering Phenergan. Given the dangers of the IV push method, the verdict in Ms. Levine's favor advanced, not undermined,

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[10]*See also, e.g., Sprietsma v. Mercury Marine*, 537 U.S. 51, 64 (2002); *Goodyear Atomic Corp. v. Miller*, 486 U.S. 174, 185-86 (1988).

federal health and safety objectives. *See Bates*, 544 U.S. at 450-51. Moreover, because FDA regulations expressly allow Wyeth to warn against use of the IV push method, Ms. Levine's recovery – premised on a failure to provide that warning – cannot be an obstacle to the accomplishment of such objectives. *See* Pet. App. 9a-19a. Thus, Ms. Levine's claim – whether viewed under the "impossibility" or "obstacle" prong of conflict preemption – is not preempted, and the question whether the Vermont Supreme Court mis-spoke on the nuances of implied preemption doctrine is an academic issue unworthy of review.[11]

2. Even assuming that the FDA's 2006 preamble is entitled to retroactive effect, *see supra* at 21-23, and that it applies to the facts here, *see supra* at 18-21, it should not be accorded deference for several independent reasons. Thus, the preamble provides no basis for finding preemption.

First, administrative agencies, because they are creatures of the executive branch, do not have the power to regulate with the force of law unless Congress has delegated that power to them. *See Gonzales v. Oregon*, 126 S. Ct. 904, 915-16 (2006). As noted above (at 7), Congress declined to provide a federal damages remedy in the FDCA precisely because state-law

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[11]Wyeth's reliance on *Geier v. American Honda Motor Co., Inc.*, 529 U.S. 861 (2000), is misplaced. There, the Court found that a damages suit premised on an automaker's failure to install airbags was an obstacle to the accomplishment of federal regulatory objectives because the agency had considered requiring airbags alone, but ultimately decided that automakers should have the flexibility to choose from a variety of passive restraints. *Id.* at 875-82. The more apt authority is the Court's post-Geier decision in *Sprietsma v. Mercury Marine*. There, a damages action premised on a boat manufacturer's failure to install a propeller guard was not preempted where the federal agency considered whether to require such guards but ultimately took no action on the topic. 537 U.S. at 60-62, 65-67. *Sprietsma* applies here in spades because the FDA did not consider, let alone reject, a warning precluding the use of IV push.

damages remedies were available. Therefore, Congress hardly can be said to have authorized the FDA to supersede damages remedies traditionally provided by the states. *See also Adams Fruit v. Barrett*, 494 U.S. 638, 650 (1990) (declining to defer to agency's view regarding preemptive reach of federal statute's right of action, and noting that, despite agency's authority to issue relevant safety standards, "an agency may not bootstrap itself into an area in which it has no jurisdiction.") (quoting *Federal Maritime Comm'n v. Seatrain Lines, Inc.*, 411 U.S. 726, 745 (1973)).

Second, the preamble lacks the requisite formality to be accorded deference. *See United States v. Mead Corp.*, 533 U.S. 218, 228 (2001). The preamble is not part of the FDA's new labeling regulation and does not appear in the Code of Federal Regulations. *See id.* at 229-30. Indeed, FDA regulations treat a regulatory preamble as an "advisory opinion," 21 C.F.R. § 10.85(d)(1), which cannot bind the public in an administrative or court proceeding because it is not "a legal requirement." *Id.* § 10.85(j).

Third, even assuming that a regulatory preamble could in some circumstances add to the preemptive force of federal law, the 2006 preamble cannot do so because its views on preemption were not subject to the notice-and-comment process required to give them such force under the Administrative Procedure Act, 5 U.S.C. § 553. As explained above, when the FDA proposed the new labeling regulations, it stated that they would not preempt state law. 65 Fed. Reg. at 81103 ("FDA has determined that this proposed rule does not contain policies that have federalism implications or that preempt State law."). Although the agency asked whether the "Highlights" section of the proposed labeling rule should be revised to address liability concerns, *id.* at 81086, the agency never intimated that it was contemplating a position that embraced preemption of any state-

law tort claims, whether or not related to the "Highlights" section, and thus it did not provide the notice demanded by section 553. *See, e.g., Envtl. Energy Project v. EPA*, 425 F.3d 992, 996 (D.C. Cir. 2005) (citing cases) (final rule must be "logical outgrowth" of proposed rule, which must provide reasonable basis to anticipate change and not require public to "divine [agency's] unspoken thoughts") (citation omitted).

Fourth, deference is often inappropriate where an agency's position lacks consistency. *See Mead*, 553 U.S. at 228. Here, as noted above (at 7-8), the FDA originally took a no-preemption position in the very rulemaking that resulted in the 2006 preamble, and, until recently, it has consistently maintained that federal drug regulation does not affect state-law damages liability. The Court repeatedly has refused to give weight to agency flip-flops regarding tort preemption. *See Bates*, 544 U.S. at 449 ("The notion that FIFRA contains a nonambiguous command to pre-empt the types of tort claims that parallel FIFRA's misbranding requirements is particularly dubious given that just five years ago the United States advocated the interpretation that we adopt today."); *Norfolk Southern Ry. Co. v. Shanklin*, 529 U.S. 344, 356 (2000). The government's position need not be immutable, but it cannot change willy-nilly, as it has here, without the agency providing concrete examples showing that tort recoveries have undermined federal drug regulation.

Finally, deference is inappropriate because the FDA's views are unpersuasive. *See Mead*, 553 U.S. at 228. As noted, the FDCA permits preemption of state law only when the two are in "direct" conflict. Assuming that a state-law failure-to-warn damages verdict may ever constitute such a direct conflict, it cannot do so when the agency's own regulations require manufacturers to revise their labels to protect the public health and permit such changes without prior agency approval.

CONCLUSION

The petition for a writ of certiorari should be denied.

Respectfully submitted,

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IN THE

Supreme Court of the United States

WYETH,

Petitioner,

v.

DIANA LEVINE,

Respondent.

ON PETITION FOR A WRIT OF CERTIORARI TO THE SUPREME COURT OF THE STATE OF VERMONT

REPLY BRIEF

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LIST OF PARTIES

Petitioner's list of parties was set forth at page *ii* of its Petition for Writ of Certiorari, and there are no amendments to that statement.

CORPORATE DISCLOSURE STATEMENT

Petitioner's corporate disclosure statement was set forth at page *ii* of its Petition for Writ of Certiorari, and there are no amendments to that statement.

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1 Kenneth Culp Davis, *Administrative Law Treatise* § 5.09 (1958) 10

Respondent's Brief in Opposition ("BIO") fails to overcome the demonstration by Wyeth and supporting amici that the issues arising from the facts of this case warrant the Court's immediate review. Specifically, the federal preemption issues raised by Wyeth's Petition are of great doctrinal and practical importance, particularly given the deep-seated division of views reflected in the split Vermont Supreme Court opinion. Respondent has no substantial answer to these points, which call for a grant of the Petition under this Court's Rule 10(c).

Instead, Respondent seeks to undermine this case as a "vehicle" for presenting these issues by distorting relevant preemption precedent, misdescribing FDA's regulation of Phenergan, and mischaracterizing the nature of the Vermont Supreme Court's findings and the overall regulatory regime under the Federal Food, Drug, and Cosmetic Act (the "FDCA"), including misrepresenting the effect of both the section 202 preemption clause in the Drug Amendments of 1962 and FDA's 2006 Preemption Preamble. *See* Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products, 71 Fed. Reg. 3922 (Jan. 24, 2006). Each of these contentions lacks merit.

I. Respondent Ignores The Deep Divisions In The Lower Courts Concerning The Preemptive Effect Of FDA's Labeling Judgments.

Respondent portrays a false uniformity in lower court decisions by claiming that "[n]o appellate court – federal or state – has ever held that the FDA's drug approval authority or its authority over drug labeling preempts a state-law tort suit[.]" BIO 13. Respondent conveniently ignores the California Supreme Court's decision in *Dowhal v. SmithKline Beecham Consumer Healthcare*, 88 P.3d 1 (Cal. 2004) (discussed at length in the Brief of Amicus Curiae Pharmaceutical Research and Manufacturers Association of America Supporting Petitioner 17-19 ("PhRMA Brief")). It also ignores a long line of federal appellate cases clearly endorsing conflict preemption to foreclose tort actions based on FDA's analogous Pre-Marketing Approval ("PMA") of medical devices. For example, the Third Circuit recently held that:

> Because the design of the HeartMate, the labeling and the instructions for its use, and the specification of the suture and its location when the HeartMate is implanted, as well as the other requirements imposed by the PMA, were the subject of extensive consideration by the FDA leading up to its PMA approval, any finding in [plaintiff] Horn's favor based on her general claims of negligence of defective design and manufacture – be it by a jury or a court – would . . . "stand as an obstacle to the accomplishment and execution of" the objective of the safety and effectiveness of the HeartMate specifically and would conflict with the federal requirements imposed by the PMA.

Horn v. Thoratec Corp., 376 F.3d 163, 169 (3d Cir. 2004) (citation omitted); *see also Riegel v. Medtronic, Inc.*, 451 F.3d 104, 122 (2d Cir. 2006), *cert. pending and Solicitor General's views invited*, 127 S. Ct. 575 (2006); *Brooks v. Howmedica, Inc.*, 273 F.3d 785, 798-99 (8th Cir. 2001) 'observing that any conflicting requirements sought by the plaintiff threatened "to interfere with . . . specific federal interest[s]" and were preempted); *Martin v. Medtronic, Inc.*, 254 F.3d 573, 584 (5th Cir. 2001); *Kemp v. Medtronic, Inc.*, 231 F.3d 216, 226-27 (6th Cir. 2000); *Mitchell v. Collagen Corp.*, 126 F.3d 902, 911 (7th Cir. 1997).

Respondent also ignores the ongoing division of views stimulated in the lower courts by FDA's Preemption Preamble. *Compare In re Bextra & Celebrex Mktg. Sales Practices & Prod. Liab. Litig.*, No. 05-1699, 2006 WL 2374742 (N.D. Cal. Aug. 16, 2006) *with Cartwright v. Pfizer, Inc.*, 369 F. Supp. 2d 876 (E.D. Tex. 2005); *see also* Pet. for Writ of Cert. ("Pet.") 16-17. Far from being settled, this area of the law is in turmoil. Letting the issue of preemption under the FDCA continue to percolate through the lower courts could risk erroneous decisions in tens of thousands of pending cases. Pet. 13-14.

II. Respondent Misdescribes FDA's Regulation Of Phenergan.

Respondent erroneously argues that "Ms. Levine's recovery was *not* based on a labeling judgment different from a labeling judgment made by the FDA." BIO 14-15. Indeed,

Respondent contends that "use of the IV push method is not . . . even mentioned" on Phenergan's label, BIO 4, that FDA's consideration of Phenergan's labeling through 1987 "did not concern the method of administration of Phenergan in general, or the IV push method in particular," BIO 9, and that "no record evidence suggests that the FDA even considered the particular safety ramifications of the IV push method for Phenergan administration," BIO 17. These unsupported assertions, however, are belied by (a) the requirements of the FDCA, (b) Phenergan's FDA-approved label itself, and (c) the established administrative record of FDA's comprehensive evaluation of the safety issues arising from arterial exposure to Phenergan.

Since 1938 – long before Phenergan's approval – the FDCA has required FDA to find a drug to be "safe for use under the conditions prescribed, recommended or suggested in the proposed labeling thereof" before approving it for marketing. 21 U.S.C. § 355(d); *see also id.* § 355(e) (requiring FDA to withdraw drug from market where "new evidence . . . shows that such drug is not shown to be safe for use under the conditions of use upon the basis of which the application was approved"). Thus, FDA's approval of a prescription drug and its labeling establishes FDA's judgment that the methods of administration "prescribed, recommended or suggested" in that labeling permit safe use of the drug.

Despite Respondent's contrary claim that Phenergan's labeling does not mention IV push injection, BIO 4, the label's "Dosage and Administration" section expressly states that the "TUBEX® Sterile Cartridge-Needle Unit" injection apparatus disclosed in the labeling "is suitable for substances to be administered *intravenously or intramuscularly*" and specifically describes a method for "push" injection using that apparatus as follows: "Method of Administration is the same as with conventional syringe. Remove needle cover by grasping it securely, twist and pull. Introduce needle into patient, aspirate by pulling back slightly on the plunges, and inject." App. 168a (emphasis added). The label also expressly describes the increased efficacy of IV, as opposed to intramuscular, injection, App. 167a, states that intravenous administration "is well tolerated, but use of this route is not without some hazard,"

App. 168a, and makes clear that "deep intramuscular injection" is "[t]he preferred parenteral route of administration," App. 168a. It even expressly describes the hierarchy of *IV administration* options – *i.e.*, IV push injection versus IV drip – advising that "[w]hen used intravenously . . . it is preferable to inject through the tubing of an intravenous infusion set that is known to be functioning satisfactorily." App. 168a.

The administrative record of FDA's ongoing review of Phenergan likewise demonstrates that, contrary to Respondent's arguments, FDA and its Advisory Committee not only were well aware of the risks of arterial exposure but were the driving force behind many of Phenergan's labeling statements concerning those risks as well as the hierarchy of IV and other administration methods. *See, e.g.*, App. 147a (recommending preservation of warnings regarding intra-arterial injection); App. 148a (recommending addition of instruction that if Phenergan is administered intravenously, it should be "injected into a satisfactorily functioning intravenous set"); *see also* App. 142a, 143a, 151a, 152a, 153a, 162a. Thus, the record clearly demonstrates that FDA determined that Wyeth's label should include IV push injection as a less-preferred, but permissible, alternative. The crux of the present dispute is the conflict between that FDA determination and the imposition by Vermont's judicial process of a requirement that IV push injection be proscribed. *Compare* BIO 1 *with* Pet. 17.

III. Respondent Cannot Evade The Direct Collision Of Judgment Between FDA And Vermont.

Respondent attempts to avoid the diametric collision of federal and state judgment on the safety of IV push injection by pointing to the Vermont Supreme Court's conclusion that Wyeth failed to prove that FDA had considered, and would have rejected, a proposed label change to foreclose IV push injection. BIO 2, 14-15, 21. Above and beyond the fact that the Phenergan label itself, as well as the administrative record, establish that FDA had carefully considered the safety implications of IV and other forms of administration and devised a hierarchy of administration options, *see supra* Part II,

that argument is without merit. Even assuming that Wyeth would have had a basis for seeking such change, the Vermont Supreme Court, addressing preemption as a matter of law, App. 6a, committed a fundamental legal error by seeking to determine what FDA might have done if hypothetically presented with a proposed label change. *See Buckman Co. v. Plaintiffs' Legal Comm.*, 531 U.S. 341, 349-51 (2001) (shielding FDA decisional processes from state law intrusion). The Vermont Court's insistence that a conflict could be established only by a showing that Petitioner unsuccessfully sought FDA approval for the warning that Respondent advocated under Vermont law would produce the same disruption of regulatory relationships that this Court foreclosed in *Buckman*.

The error presented by Petitioner is not, as Respondent would have it, "an erroneous factual finding." *See* BIO 14-15, 21. Rather, that error lies in the legal standard for determining the federal-state conflict on which preemption is based. *See Steele v. Depuy Orthopaedics, Inc.*, 295 F. Supp. 2d 435, 446 (D.N.J. 2003) (explaining that "whether the FDA's approval of a PMA supplement imposes requirements on a particular device is a question of law to be determined by the Court, not a question of fact for the jury"). Under *Buckman*, that conflict must be assessed on the administrative record as it exists rather than on the basis of speculation whether the agency would or would not have modified it. *See Buckman*, 531 U.S. at 349-51.

Respondent also argues that Wyeth could have overcome FDA's judgment of record, and thus conformed to Vermont's standard of care, by unilaterally changing its label under FDA's "changes being effected," or "CBE," regulation. BIO 12, 24 (citing 21 C.F.R. § 314.70(c)(6)(iii)). But Respondent's defense of the Vermont Supreme Court's out-of-context reading of that regulation, App. 19a, flies in the face of FDA's comprehensive regulatory regime. Petitioner's interpretation, in contrast, accords with the overall FDCA framework and the weight of judicial authority, which limit the CBE regulation to exigent circumstances where "new information" on a drug necessitates an immediate labeling change. Pet. 19.

Respondent's reliance on 21 C.F.R. § 201.80(e), BIO 24-25, to suggest that FDA regulations mandated that Wyeth foreclose IV push injection only confirms Petitioner's analysis. Section 201.80(e) has both a temporal component (labeling to be revised "as soon as" there is an appropriate basis), and a substantive component ("reasonable evidence" of an associated hazard). At the time of Respondent's injury, FDA had been long aware of the risks of arterial exposure, had extensively regulated the statements on Phenergan's labeling concerning the hierarchy of administration options in light of those risks, and had even rejected a proposed warning change by Wyeth purporting to respond even more specifically to the "reasonable evidence" on arterial exposure in its possession. Respondent's contention effectively would impose the absurd requirement on Wyeth repeatedly to seek labeling changes for every conceivable permutation of language concerning a particular risk – even if FDA had known of that risk for decades and had previously rejected proposed changes designed to address that risk – and is clearly untenable. *See, e.g., Dowhal*, 88 P.3d at 10 (explaining that the "warning continues to be binding until the *new data* emerges and a change is requested" (emphasis added)); *McNellis ex rel De Angelis v. Pfizer, Inc.*, No. 05-1286, 2006 WL 2819046, at *6 (D.N.J. Sept. 29, 2006) (Section 201.80(e) is triggered "as soon as *new evidence* of a serious hazard exists." (emphasis added)).

In a further effort to avoid impossibility preemption, Respondent suggests that there can be no conflict generated by the legal duty imposed on Wyeth because Vermont "does not require Wyeth to alter its conduct but only to pay damages to Ms. Levine." BIO 25. Even apart from the fact that this contention contradicts the clear intention of the Vermont Supreme Court, App. 15a (concluding that "state common law duty may encourage departure from a label that the FDA has approved in great detail"), it misstates this Court's settled preemption jurisprudence. *See San Diego Bldg. Trades Council v. Garmon*, 359 U.S. 236, 247 (1959) (explaining that "regulation can be as effectively exerted through an award of damages as through some form of preventive relief" and that "[t]he obligation to pay compensation can be, indeed is designed to

be, a potent method of governing conduct and controlling policy"); *Cipollone v. Liggett Group, Inc.*, 505 U.S. 504, 521-22 (1992) (plurality opinion) (explaining that "since *Erie R. Co. v. Tompkins*" the Court has "recognized the phrase 'state law' to include common law as well as statutes and regulations.").[1]

IV. Respondent Cannot Evade Consideration Of Obstacle Conflict Preemption Under The FDCA Or The Degree Of Deference To Be Accorded FDA's Preamble.

Turning to obstacle preemption, Respondent recites, without providing any supporting analysis whatsoever, the Vermont Supreme Court's conclusions that the application of this strand of conflict preemption to prescription drug labeling cases is entirely foreclosed by section 202 of the Drug Amendments of 1962, Pub. L. No. 87-781, 76 Stat. 780 (1962). BIO 25. It also agreed with the Vermont Court's holding that FDA's 2006 Preamble analysis of the obstructive effect of state tort judgments on its regulatory regime should be given no weight. BIO 26-28. Respondent again errs in both contentions.

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1. Respondent's reliance on *Bates v. Dow Agrosciences LLC*, 544 U.S. 431 (2005) for the proposition that no impossibility of compliance can arise from a conflict between a federal duty and a state common law tort duty is in error. BIO 25. In *Bates*, this Court interpreted the term "requirement" in a federal preemption clause barring States from imposing "requirements" that differed from analogous federal requirements. 544 U.S. at 443. While the Court explained that "requirements" should be determined by "an examination of the common law duty at issue," *id.* at 445, and that the lower court was wrong to blindly assume "that any event, such as a jury verdict, that might 'induce' a pesticide manufacturer to change its label should be viewed as a requirement," *id.* at 443, it was careful to explain that "the term 'requirements' in § 136v(b) reaches beyond positive enactments, such as statutes and regulations, to embrace common-law duties." *Id.* (citation omitted). Hence, the common-sense understanding that each statutory preemption clause must be reviewed to determine its reach does not in any way undermine the settled rule that federal law preempts any state law that conflicts, irrespective of whether the state law is a statute, regulation, or jury award. *See, e.g., Int'l Paper Co. v. Ouellette*, 479 U.S. 481, 494 (1987) ("[T]he application of Vermont [nuisance] law against IPC would allow respondents to circumvent the NPDES permit system, thereby upsetting the balance of public and private interests so carefully addressed by the Act.").

As explained in the Petition, the text and legislative history of section 202 foreclose field preemption but expressly preserve preemption claims in cases involving "direct and positive conflict[s]." Pet. 23-24. Congress's choice of the phrase "direct and positive conflict" – a phrase with well-accepted roots in obstacle preemption – is telling. Because of both Congress's preservation of obstacle preemption by its use of a phrase long associated with obstacle preemption claims and the statutory mandate to apply the "unless" clause in section 202, the courts are obligated to consider whether the duty imposed on Wyeth by Vermont law "stands as an obstacle to the accomplishment and execution of the full purposes and objectives of Congress" as implemented by FDA under the FDCA. *Hines v. Davidowitz*, 312 U.S. 52, 67 (1941); *see also Bates v. Dow Agrosciences LLC*, 544 U.S. 431, 457 (2005) (Thomas, J., concurring in part, dissenting in part) (concluding that statutory preemption language applies as written without regard to any contrary presumption favoring state law). Where, as here, Vermont seeks to foreclose a treatment option that FDA has left open, Vermont law stands in "direct and positive" conflict with FDCA.[2] It simply defies logic to suggest that Congress, when it empowered FDA to protect the public health and safety, intended at the same time to allow state law to frustrate FDA in achieving that statutory objective.

Respondent's further efforts to support the Vermont Supreme Court's misguided decision to accord "no deference"

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2. Respondent's reliance on *Sprietsma v. Mercury Marine*, 537 U.S. 51 (2002), is misplaced. BIO 26. That case merely held that the Coast Guard's decision not to adopt a particular regulation could not be viewed as "the functional equivalent of a regulation prohibiting all States and their political subdivisions from adopting such a regulation." *Sprietsma*, 537 U.S. at 66. Moreover, the Solicitor General and counsel for the Coast Guard expressly had informed the Court that "the agency does not view the 1990 refusal to regulate or any subsequent regulatory actions by the Coast Guard as having any pre-emptive effect." *See id.* at 68. Here, FDA has affirmatively regulated every aspect of Phenergan's labeling – including IV injection in particular – since its introduction to the market in 1955. Pet. 6-9. Moreover, FDA specifically commanded Wyeth to retain a particular instruction concerning IV administration instead of permitting Wyeth to alter the instructions in a way that would further encourage IV drip administration over IV push administration. App. 160a-163a.

to FDA's Preemption Preamble, on grounds not reached by that court, App. 25a-26a, are similarly unpersuasive. BIO 26. Respondent creates and attacks a straw man by contending that FDA was seeking to enact a legislative rule in the Preamble. BIO 21-23. To the contrary, as explained in the Petition, the Preamble sets forth FDA's longstanding construction of its own regulations and the impact of state-imposed duties on the accomplishment of FDA's regulatory purposes. Pet. 27-29. FDA's interpretation, addressing the FDCA, clearly governs conflicting duties arising before 2006 as well as thereafter.

FDA's publication readily falls within the definition of an interpretive rule. *See, e.g., United Techs. Corp. v. EPA*, 821 F.2d 714, 718 (D.C. Cir. 1987) ("An interpretive rule simply states what the administrative agency thinks the [underlying] statute means, and only reminds affected parties of existing duties." (internal quotations and citations omitted) (alteration in original)).[3] Unlike legislative rules, interpretive rules do not raise retroactivity concerns. *See, e.g., Griffon v. U.S. Dep't of Health & Human Servs.*, 802 F.2d 146, 151 (5th Cir. 1986)

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3. As an interpretive rule, the Preamble also is not subject to the formality of "notice and comment" that Respondent seeks to invoke. BIO 27. Indeed, deference has been afforded to interpretative rules of varying formality. *See, e.g., Geier v. Am. Honda Motor Co.*, 529 U.S. 861, 883 (2000); *Auer v. Robbins*, 519 U.S. 452, 453 (1997). And, with respect to FDA, this Court has made clear that its expert judgments are entitled to particular deference. *See, e.g., Weinberger v. Bentex Pharms., Inc.*, 412 U.S. 645, 653-54 (1973) ("The determination whether a drug is . . . safe and effective" is "peculiarly suited to initial determination by the FDA."). Respondent's further argument that FDA has taken inconsistent interpretive positions on preemption is equally mistaken. Respondent seizes on a 2000 FDA statement that prescription drug labeling "does not preempt State law." BIO 8 (quoting 65 Fed. Reg. 81,802, 81,103 (2000)). But this was merely a statement recognizing that field preemption does not apply – it was not an indication that the States are free to override specific FDA determinations to create direct and positive federal-state conflicts. To the contrary, FDA had consistently maintained, both before and after 2000, that state-law standards of care that differ from federal labeling judgments pose an obstacle to the federal regime. *See generally* Brief for Amicus Curiae The United States of America, *Colacicco v. Apotex, Inc.*, 432 F. Supp. 2d 514 (E.D. Pa. 2006) (No. 05-05500).

("Interpretative rules do not require notice and comment rulemaking, 5 U.S.C. § 553(b)(3)(A), and cannot be retroactive because they effectuate the intent of the statute."); *Appalachian States Low-Level Radioactive Waste Comm'n v. O'Leary*, 93 F.3d 103, 113 (3d Cir. 1996) ("[R]etroactivity concerns are irrelevant to this case. The Secretary's ruling was interpretive. It therefore did not alter existing rights or obligations; it merely clarified what those existing rights and obligations had always been."); *see also* 1 Kenneth Culp Davis, *Administrative Law Treatise* § 5.09 (1958).

Recognizing the persuasiveness of FDA's Preamble and the agency's expertise in assessing how the public health would be affected by imposing state-created duties on manufacturers, the better-reasoned court decisions have accorded compelling weight to FDA's analysis. Pet. 28-30. This Court should review this case and support that sound result.

CONCLUSION

For the foregoing reasons and for the reasons set forth in the petition, this Court should grant the petition for writ of certiorari.

Respectfully submitted,

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In the Supreme Court of the United States

WYETH, PETITIONER

v.

DIANA LEVINE

ON PETITION FOR A WRIT OF CERTIORARI TO THE SUPREME COURT OF VERMONT

BRIEF FOR THE UNITED STATES AS AMICUS CURIAE

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QUESTION PRESENTED

Whether state-law tort claims are preempted to the extent that they would impose liability for a drug manufacturer's use of labeling that the Food and Drug Administration approved after being informed of the relevant risk.

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In the Supreme Court of the United States

No. 06-1249

WYETH, PETITIONER

v.

DIANA LEVINE

ON PETITION FOR A WRIT OF CERTIORARI TO THE SUPREME COURT OF VERMONT

BRIEF FOR THE UNITED STATES AS AMICUS CURIAE

This brief is filed in response to the Court's order inviting the Solicitor General to express the views of the United States. In the view of the United States, the petition for a writ of certiorari should be held pending this Court's decisions in *Riegel* v. *Medtronic, Inc.*, No. 06-179 (argued Dec. 4, 2007), and *Warner-Lambert Co., LLC* v. *Kent*, cert. granted, No. 06-1498 (Sept. 25, 2007), and then disposed of as appropriate in light of the decisions in those cases.

STATEMENT

1. Under the Federal Food, Drug, and Cosmetic Act (FDCA or Act), 21 U.S.C. 301 *et seq.*, a drug manufacturer may not market a new drug unless it has submitted a new drug application to the Food and Drug Administration (FDA) and received the agency's approval. 21 U.S.C. 355(a). An application must contain, among other things, "the labeling proposed to be used for such drug,"

21 U.S.C. 355(b)(1)(F) (Supp. V 2005); see 21 C.F.R. 314.50(c)(2)(i) and (e)(2)(ii); "full reports of investigations which have been made to show whether or not such drug is safe for use and whether such drug is * * * effective in use," 21 U.S.C. 355(b)(1)(A) (Supp. V 2005); and "a discussion of why the benefits exceed the risks [of the drug] under the conditions stated in the labeling," 21 C.F.R. 314.50(d)(5)(viii); see 21 C.F.R. 314.50(c)(2)(ix).

The FDCA also requires that drugs not be misbranded. 21 U.S.C. 331(a) and (b). A drug is misbranded if, among other things, the drug's "labeling is false or misleading in any particular;" the labeling does not provide "adequate directions for use" or certain "adequate warnings;" the drug "is dangerous to health when used in the dosage or manner, or with the frequency or duration prescribed, recommended, or suggested in the labeling thereof;" or the labeling does not comply with certain FDA regulations. 21 U.S.C. 352(a), (f) and (j). FDA has established specific requirements for prescription drug labeling. 21 C.F.R. Pt. 201.

FDA will approve a new drug application if it finds, among other things, that (i) the drug is "safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof," (ii) there is "substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling thereof," and (iii) the proposed labeling is not "false or misleading in any particular." 21 U.S.C. 355(d).

After a drug has been approved and marketed, the manufacturer must investigate and report to FDA any adverse events associated with use of the drug in humans, 21 C.F.R. 314.80, and must periodically submit

any new information that may affect FDA's previous conclusions about the safety, effectiveness, or labeling of the drug, 21 C.F.R. 314.81. See 21 U.S.C. 355(k) (post-approval reporting and record-keeping requirements); Food and Drug Administration Amendments Act of 2007, Pub. L. No. 110-85, § 901 *et seq.*, 121 Stat. 922 (enhancing FDA's authority to require postmarket studies and surveillance). FDA "shall" withdraw its approval of an application if it finds, among other things, that the drug is not safe or effective under the conditions of use specified in the drug's labeling. 21 U.S.C. 355(e).

Following FDA's approval of an application, the manufacturer generally may not make changes to the drug, including "[c]hanges in labeling," without first submitting a supplemental application to FDA and securing the agency's prior approval for the change. 21 C.F.R. 314.70(b)(2)(v)(A). A manufacturer must submit such a supplemental application "to include a warning about a clinically significant hazard as soon as there is reasonable evidence of a causal association with a drug." 21 C.F.R. 201.57(c)(6). "An applicant may ask FDA to expedite its review of a supplement for public health reasons." 21 C.F.R. 314.70(b)(4). In addition, a manufacturer may change a drug's labeling at the same time that it submits a supplemental application to FDA, without waiting for the agency's approval of the change, if, among other things, the change "add[s] or strengthen[s]" a warning or a statement about administration of the drug in order to promote safety. 21 C.F.R. 314.70(c)(6)(iii)(A) and (C). FDA interprets that regulation to permit changes without prior approval only to address "newly discovered risks." 47 Fed. Reg. 46,623 (1982). If a manufacturer makes a change before receiving FDA's approval, the agency may later reject the

change and order the manufacturer to cease distribution of the changed product. 21 C.F.R. 314.70(c)(7).

2. After FDA approved petitioner's new drug application for the anti-nausea drug Phenergan, petitioner informed FDA of adverse events in which Phenergan apparently was inadvertently injected intra-arterially, resulting in gangrene and amputation. See, *e.g.*, Pet. App. 139a-140a (1967 report). Over the ensuing years, FDA and petitioner engaged in back-and-forth communications concerning the appropriate labeling to address the risks presented by inadvertent intra-arterial injection. See, *e.g.*, *id.* at 141a-166a. As part of its deliberations, FDA convened an expert advisory committee to consider that question. *Id.* at 144a, 147a-148a.

As of 2000 (when the events giving rise to this suit occurred), the FDA-approved labeling stated, in part, that "[u]nder no circumstances should Phenergan Injection be given by intra-arterial injection due to the likelihood of severe arteriospasm and the possibility of subsequent gangrene." Pet. App. 167a. The labeling went on to explain that the "preferred" method of administering the drug is "by deep intramuscular injection," because intravenous administration can result, in some circumstances, in inadvertent intra-arterial injection. *Ibid.* For circumstances in which the drug is injected intravenously, the labeling described in detail how such injection should be done, in order "to avoid * * * inadvertent intra-arterial injection." *Ibid.*

3. In April 2000, respondent sought treatment at a health center for headache and nausea. Pet App. 2a. The health center's staff first administered Phenergan to respondent by intra-muscular injection. *Ibid.* When respondent's nausea continued, the staff administered a second dose of Phenergan by intravenous injection into

her arm. *Ibid.* The intravenous injection was made by a procedure the parties refer to as IV push, whereby the Phenergan solution was not dripped through a free-flowing bag, but instead was directly injected into respondent's arm. See *id.* at 2a, 52a. The IV push apparently resulted in inadvertent arterial injection, which damaged respondent's arteries, caused gangrene, and required amputation of her hand and forearm. *Id.* at 2a.

Respondent brought and settled an action against the health center where she had received the injection of Phenergan. Pet. App. 50a. She also sued petitioner in a Vermont state court, asserting negligence and failure-to-warn claims premised on alleged inadequacies in the drug's labeling. *Id.* at 3a. Respondent asserted that "the label should not have allowed IV push as a means of administration, as it was safer to use other available options, such as intramuscular injection or administration through the tubing of a hanging IV bag." *Ibid.* After the trial court rejected petitioner's preemption defense, *id.* at 49a-74a, the jury found in respondent's favor, and the trial court entered judgment in the amount of $6,774,000, *id.* at 3a.

4. a. The Vermont Supreme Court affirmed. Pet. App. 1a-34a. It interpreted 21 C.F.R. 314.70(c) to "allow unilateral changes to drug labels whenever the manufacturer believes it will make the product safer." *Id.* at 13a. In the court's view, Section 314.70(c) was crucial to the preemption analysis: "While specific federal labeling requirements and state common-law duties might otherwise leave drug manufacturers with conflicting obligations, [Section] 314.70(c) allows manufacturers to avoid state failure-to-warn claims without violating federal law" by making unilateral changes to FDA-approved labeling. *Id.* at 11a.

The Vermont Supreme Court also relied on a provision in the 1962 amendments to the FDCA that states that "[n]othing in th[ose] amendments * * * shall be construed as invalidating any provision of State law * * * unless there is a direct and positive conflict between such amendments and such provision of State law." Drug Amendments of 1962, Pub. L. No. 87-781, § 202, 76 Stat. 793. The court construed that provision to limit preemption to circumstances in which it would be physically impossible for a manufacturer to comply with both federal and state law. Pet. App. 21a. Here, the court determined, there was no such impossibility because there was no indication that FDA would have rejected a supplemental application seeking to strengthen the warning under Section 314.70(c). *Id.* at 17a.

b. Chief Judge Reiber dissented. Pet. App. 35a-48a. He explained that respondent's state-law claims conflict with federal law because, while "FDA concluded that the drug—with its approved methods of administration and as labeled—was both safe and effective," the "jury concluded that the same drug—with its approved methods of administration and as labeled—was 'unreasonably dangerous.'" *Id.* at 35a (quoting *Town of Bridport* v. *Sterling Clark Lurton Corp.*, 693 A.2d 701, 704 (Vt. 1997)). Supporting that conclusion, in the Chief Judge's view, is the fact that FDA does not merely establish minimum safety standards, but instead "balances its assessment of a drug's safety against concerns for the drug's efficacy, taking into account that a safer but less effective drug is not necessarily best for the public health overall." *Id.* at 47a. With respect to drug labels, the Chief Judge explained, "FDA considers not only what information to include, but also what to exclude,"

in part because overwarning can do more harm than good. *Ibid.*

The Chief Judge also took issue with the majority's understanding of Section 314.70(c). Pet. App. 39a-41a. He explained that the regulation "allow[s] manufacturers to address newly discovered risks," but "does not allow manufacturers to simply reassess and draw different conclusions regarding the same risks and benefits already balanced by the FDA." *Id.* at 40a.

DISCUSSION

Petitioners' claims are impliedly preempted by the FDCA because they challenge labeling that FDA approved, after being informed of the relevant health risk, based on its expert weighing of the risks and benefits of requiring additional or different warnings. The Vermont Supreme Court's contrary conclusion rests on its mistaken view that an FDA regulation, 21 C.F.R. 314.70(c), "allow[s] unilateral changes to drug labels whenever the manufacturer believes [the changes] will make the product safer." Pet. App. 13a. That interpretation of the regulation is wrong, because Section 314.70(c) permits unilateral changes based only on newly available information, not based on information that was previously available to FDA, such as the risk at issue here.

While the Vermont Supreme Court's decision is wrong, it does not warrant plenary review at this time. The decision below does not squarely conflict with any decision of a federal court of appeals or another state supreme court. Moreover, this Court's decisions in two pending FDA preemption cases—*Riegel* v. *Medtronic, Inc.*, No. 06-179 (argued Dec. 4, 2007), and *Warner-Lambert, LLC* v. *Kent*, cert. granted, No. 06-1498 (Sept.

25, 2007)—may shed significant light on the question presented in this case. Accordingly, the Court should hold the petition in this case pending its decisions in *Riegel* and *Warner-Lambert*, and then dispose of the petition as appropriate in light of its disposition of those cases.

A. Respondent's Claims Are Impliedly Preempted

Federal law preempts state laws that conflict with federal law, including state laws that either "make it 'impossible' for private parties to comply with both state and federal law," *Geier* v. *American Honda Motor Co.*, 529 U.S. 861, 873 (2000), or that "stand[] as an obstacle to the accomplishment and execution of the full purposes and objectives of Congress," *Hines* v. *Davidowitz*, 312 U.S. 52, 67 (1941). Because respondent's claims challenge labeling that FDA approved after being informed of the relevant risk, they conflict with FDA's approval of the labeling and are therefore preempted.

1. FDA's approval of a drug, including its labeling, generally preempts state law claims challenging the drug's safety, efficacy, or labeling

a. FDA may approve a new drug application only if it determines, among other things, that (i) the drug is "safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof," (ii) there is "substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling thereof," and (iii) the proposed labeling is not "false or misleading in any particular." 21 U.S.C. 355(d). Thus, FDA specifically considers and approves a drug's labeling. Indeed, the agency's consideration of safety and effectiveness is di-

rectly tied to its consideration of "the proposed labeling," *ibid.*, in part because a drug's safety and effectiveness depend on the condition under which it is used (*e.g.*, its dosage, its method of administration, and its intended use). Labeling is "[t]he centerpiece of risk management," as it "communicates to health care practitioners the agency's formal, authoritative conclusions regarding the conditions under which the product can be used safely and effectively." 71 Fed. Reg. 3934 (2006).

FDA's review of a new drug application is similar to its premarket approval process for Class III medical devices, see 60 Fed. Reg. 39,180 (1995), which this Court has correctly described as "rigorous," *Medtronic, Inc.* v. *Lohr*, 518 U.S. 470, 477 (1996). As part of the approval process, an applicant must submit "the labeling proposed to be used for such drug," 21 U.S.C. 355(b)(1)(F) (Supp. V 2005), as well as extensive information about the composition, manufacture, and specification of the drug, any studies of the drug's pharmacological actions and toxicological effects in animals, any studies of the drug's bioavailability and pharmacokinetics in humans, any clinical investigations of the drug, and "any other data or information relevant to an evaluation of the safety and effectiveness of the drug product obtained or otherwise received by the applicant from any source." 21 C.F.R. 314.50(d); see 21 U.S.C. 355(b)(1)(A) (Supp. V 2005).

If FDA is not ultimately satisfied that a drug is safe for use under the conditions of its labeling and that there is substantial evidence that the drug is effective when used according to the labeling, FDA cannot approve the application. 21 U.S.C. 355(d). Thus, FDA's approval reflects its expert determination, based on a careful review of extensive scientific and technical infor-

mation, that a drug is safe and effective when used according to its labeling, and that the labeling satisfies federal requirements.

b. In making those determinations, FDA does not merely police minimum standards of safety, as the Vermont Supreme Court thought. See Pet. App. 19a. Instead, FDA *weighs* health benefits against health risks. See 71 Fed. Reg. at 3934; 60 Fed. Reg. at 39,180. As this Court has explained, FDA "generally considers a drug safe when the expected therapeutic gain justifies the risk entailed by its use." *United States* v. *Rutherford*, 442 U.S. 544, 555 (1979); accord *FDA* v. *Brown & Williamson Tobacco Corp.*, 529 U.S. 120, 140 (2000). FDA has, for example, approved cancer treatments that are highly toxic and thus not "safe" as that term is ordinarily used, but that are nonetheless safe in the relevant sense under the FDCA because the potential benefits to health outweigh the risks. 61 Fed. Reg. 44,413 (1996); see *Brown & Williamson*, 529 U.S. at 142.

FDA also weighs the overall health consequences of including particular instructions or warnings in a drug's labeling. As explained above, a drug's safety and effectiveness are not determined in the abstract, divorced from its labeling. See 71 Fed. Reg. at 3934. Rather, FDA requires each new drug application to contain "a discussion of why the benefits exceed the risks [of the drug] *under the conditions stated in the labeling*." 21 C.F.R. 314.50(d)(5)(viii) (emphasis added); see 21 C.F.R. 314.50(c)(2)(ix). If FDA then concludes that a drug's benefits outweigh its risks only under certain conditions, the agency may require appropriate labeling to reflect that determination. See, *e.g.*, 21 C.F.R. 314.110(a).

Moreover, a warning in a drug's labeling must strike a balance between notifying users of potential dangers

and not unnecessarily deterring beneficial uses. 71 Fed. Reg. at 3935. "Exaggeration of risk could discourage appropriate use of a beneficial drug," and thereby harm the public health. *Ibid.* In addition, excessive warnings can cause more meaningful risk information to "lose its significance." 44 Fed. Reg. 37,447 (1979); accord 71 Fed. Reg. at 3935; 65 Fed. Reg. 81,083 (2000). "Warnings about dangers with less basis in science or fewer hazards could take attention away from those that present confirmed, higher risks." *Brooks* v. *Howmedica, Inc.*, 273 F.3d 785, 796 (8th Cir. 2001), cert. denied, 535 U.S. 1056 (2002). Thus, as the dissent explained, there are "a number of sound reasons why the FDA may prefer to limit warnings on product labels." Pet. App. 47a (quoting *Brooks*, 273 F.3d at 796).

For those reasons, "FDA interprets the [FDCA] to establish both a 'floor' and a 'ceiling'" with respect to drug labeling. 71 Fed. Reg. at 3935. FDA's approval of labeling for a new drug reflects FDA's expert judgment that the labeling strikes the appropriate balance. *Ibid.* Where, as here, FDA was presented with information concerning the relevant risk, a jury's imposition of liability based on a drug's FDA-approved labeling would interfere with FDA's expert judgment.

That conflict is especially clear in this case because, as the dissent explained, any recovery under state law would be predicated on a finding that Phenergan, as labeled, was "unreasonably dangerous." Pet. App. 35a (quoting *Town of Bridport* v. *Sterling Clark Lurton Corp.*, 693 A.2d at 704). That finding would directly conflict with FDA's determination that the drug, as labeled, was safe and effective. *Id.* at 35a-36a. As such, respondent's claims are preempted. See, *e.g.*, *Geier*, 529 U.S. at 881-883 (holding that state suit seeking to impose

liability for failure to use a particular type of restraint system would stand as an obstacle to the federal agency's decision to encourage the use of a range of restraint systems); *Buckman Co.* v. *Plaintiffs' Legal Comm.*, 531 U.S. 341, 348 (2001) (holding that state-law fraud-on-FDA claim was impliedly preempted because it would interfere with FDA's ability to strike a "somewhat delicate balance of statutory objectives").

2. Federal law precluded petitioner from unilaterally changing the FDA-approved labeling

The Vermont Supreme Court erroneously interpreted 21 C.F.R. 314.70(c) to "allow unilateral changes to drug labels whenever the manufacturer believes it will make the product safer." Pet. App. 13a. As discussed above, however, the FDCA requires a manufacturer to receive FDA's approval for a new drug's labeling. 21 U.S.C. 355(a) and (d). And because FDA's approval strikes an important balance between, among other things, warning of risks and not overdeterring beneficial uses, manufacturers may *not* ordinarily modify labeling approved by FDA without first obtaining FDA's approval for the change. See 21 C.F.R. 314.70. Here, for example, FDA instructed petitioner that the "final printed labeling * * * must be identical" to the approved labeling. Pet. App. 165a. If manufacturers were free to make unilateral changes to labeling the day after FDA's approval, based on information that was previously available to FDA, the approval process would be greatly undermined and the agency's careful balancing of risks and benefits thwarted. The Vermont Supreme Court's view that "FDA approval of a drug label" is nothing more than "a first step," *id.* at 15a, is there-

fore fundamentally inconsistent with the federal regulatory framework.

Consistent with the stringent statutory and regulatory requirements for approval of a new drug in the first place, a manufacturer ordinarily must submit a supplemental application before making any changes to the drug, including changes in labeling. 21 C.F.R. 314.70(a)(2)(v). As a general rule, the manufacturer must obtain prior approval by FDA before making such changes. Section 314.70(c) provides a limited exception to that rule permitting "the holder of an approved [new drug] application [to] commence distribution of the [changed] drug product involved upon receipt by the agency of a supplement for the change" if, among other things, the change "add[s] or strengthen[s]" a warning or a statement about administration of the drug in order to promote safety. 21 C.F.R. 314.70(c)(6)(iii)(A) and (C).

As FDA explained when it proposed that regulation in 1982, however, changes may be made without prior FDA approval only "to correct concerns about *newly discovered risks* from the use of the drug." 47 Fed. Reg. at 46,623 (emphasis added). FDA explained that, "[a]lthough most changes in labeling would require the applicant to submit a supplement and obtain FDA approval before making a change," some changes that "would make available *important new information* about the safe use of a drug product" could be made upon submission of a supplemental application. *Id.* at 46,635 (emphasis added); compare FDA, *Draft Guidance for Industry and FDA Staff, Modifications to Devices Subject to Premarket Approval (PMA)* 19 (Mar. 9, 2007) <http://www.fda.gov/cdrh/ode/guidance/1584.pdf> (explaining that a manufacturer may make unilateral changes to a device subject to FDA's premarket approval only if "the

manufacturer has newly acquired safety-related information" that "was not previously considered by the FDA").

Thus, any changes to a drug's labeling without prior FDA approval still must be the subject of a supplemental application, which FDA can approve or reject, and must be based on material new information—not information that was previously available to FDA, nor even cumulative new information that does not add materially to the information that was previously available to the agency. As the dissent explained, Section 314.70(c) does not "allow manufacturers to simply reassess and draw different conclusions regarding the same risks and benefits already balanced by the FDA." Pet. App. 40a. FDA's interpretation of its own regulation is entitled to significant deference. See *Auer* v. *Robbins*, 519 U.S. 452, 461 (1997).

In this case, it does not appear that respondent relies on any material new information that was not available to FDA. The parties dispute whether FDA specifically and expressly rejected the stronger warning that respondent asserts should have been included in the labeling. See, *e.g.*, Br. in Opp. 15-17. There is and can be no dispute, however, that FDA was presented with extensive information about the dangers of accidental intra-arterial injection from intravenous administration of the drug, and that Phenergan's FDA-approved labeling provided specific guidance on how to inject the drug, either intramuscularly or intravenously, so as to reduce that risk. See p. 4, *supra*. Nor did the Vermont Supreme Court point to any marked change in the number or type of reported cases of accidental intra-arterial injection from intravenous administration that might have suggested that the risk was of a magnitude that was not

previously known at the time that FDA approved labeling that addressed that risk. Under a correct reading of Section 314.70, therefore, petitioner could not have changed the labeling without prior FDA approval, and respondent's claims are preempted.

Moreover, even when a manufacturer may make a change at the same time that it submits a supplemental application to FDA under Section 314.70(c), the supplemental application must "give a full explanation of the basis for the change." 21 C.F.R. 314.70(c)(3). The agency may then reject the change based on its own balancing of the relevant health risks and benefits. See 21 C.F.R. 314.70(c)(7). If FDA rejects the change, it may order the manufacturer to cease further distribution of the changed product. *Ibid.* Changed labeling also "remains subject to enforcement action" if FDA finds that the change "makes the labeling false or misleading." 71 Fed. Reg. at 3934; see 21 U.S.C. 352 (2000 & Supp. V 2005). Thus, whether to authorize a change is, in the end, "squarely and solely FDA's" decision. 71 Fed. Reg. at 3934. For these reasons, in practice manufacturers typically consult with FDA before making labeling changes that the manufacturer believes could appropriately be made unilaterally under 21 C.F.R. 314.70(c) while a supplemental application was pending before FDA. See 71 Fed. Reg. at 3934.

3. The 1962 amendments to the FDCA did not displace ordinary conflict-preemption principles

The Vermont Supreme Court mistakenly thought that Section 202 of the 1962 amendments to the FDCA precludes the application of ordinary conflict preemption principles in this case. See Pet. App. 21a-23a. That provision states as follows:

> Nothing in the amendments made by this Act to the Federal Food, Drug, and Cosmetic Act shall be construed as invalidating any provision of State law * * * unless there is a direct and positive conflict between such amendments and such provision of State law.

Pub. L. No. 87-781, § 202, 76 Stat. 780, 793 (1962).

At the outset, it is not clear to what extent Section 202 applies here. It is limited to "the amendments made by" the 1962 legislation. § 202, 76 Stat. 793. While those amendments broadened the scope of FDA's new drug approval process by requiring the agency to consider the efficacy as well as the safety of a drug, see § 102(b), 76 Stat. 781, FDA's new drug approval process predated the amendments, see 21 U.S.C. 355(a) and (d) (1958). Indeed, FDA approved Phenergan before 1962. See Pet. 6; Br. in Opp. 23 n.8.

Even assuming *arguendo* that Section 202 is relevant in this case, however, that provision means only that Congress did not intend the 1962 amendments to preempt the *field* of drug regulation; it does not manifest an intent to displace ordinary principles of *conflict* preemption. 71 Fed. Reg. at 3935 n.8. Indeed, Section 202 expressly contemplates preemption in circumstances involving "a direct and positive conflict." § 202, 76 Stat. 793.

The Vermont Supreme Court read that phrase to refer only to situations in which it would be impossible to comply with both federal and state law, as distinguished from situations in which state law would frustrate the purpose of the federal scheme. Pet. App. 21a-23a. That interpretation is incorrect. Before 1962, this Court had long used the phrase "direct and positive con-

flict" to refer to conflict preemption generally, not to a mere subset of such preemption. See, *e.g.*, *United Constr. Workers* v. *Laburnum Constr. Corp.*, 347 U.S. 656, 663 n.5 (1954); *Sinnot* v. *Davenport*, 63 U.S. 227, 243 (1859). In so doing, the Court contrasted "direct and positive" conflict preemption to "field" preemption, not to some subset of conflict preemption. *E.g.*, *Kelly* v. *Washington ex rel. Foss Co.*, 302 U.S. 1, 9-10 (1937). More generally, this Court has never "driven a legal wedge—only a terminological one—between 'conflicts' that prevent or frustrate the accomplishment of a federal objective and 'conflicts' that make it 'impossible' for private parties to comply with both state and federal law." *Geier*, 529 U.S. at 873.

In any event, "[t]he Court has * * * refused to read general 'saving' provisions to tolerate actual conflict both in cases involving impossibility and in 'frustration-of-purpose' cases." *Geier*, 529 U.S. at 873-874 (citation omitted). That would appear to apply, *a fortiori*, to a provision that addresses only the effect of particular amendments, not the overall permanent code. See p. 16, *supra*. Moreover, even when a statute contained a savings clause providing that "[c]ompliance with" a federal safety standard "does not exempt any person from *any* liability under common law," 15 U.S.C. 1397(k) (1988) (emphasis added), this Court held that the savings clause did not preclude the application of ordinary conflict preemption principles, including frustration of purpose principles. *Geier*, 529 U.S. at 868, 873-874. The savings clause here, which expressly provides for conflict preemption, likewise does not displace ordinary conflict preemption principles.

In the preamble to its January 2006 rule concerning the labeling of drugs, FDA explained that the govern-

ment's "long standing view[]" is that "FDA approval of labeling under the [FDCA] * * * preempts conflicting or contrary State law," especially considering that "FDA interprets the [FDCA] to establish both a 'floor' and a 'ceiling'" for labeling. 71 Fed. Reg. at 3934, 3935. The agency also "recognized[] that FDA's regulation of drug labeling will not preempt all State law actions." *Id.* at 3936. FDA then provided some specific examples of circumstances in which state laws are preempted, but it did not attempt to exhaust such circumstances. See *id.* at 3935-3936 (noting that "at least" those examples would be preempted). In this brief, the government has articulated a more generally applicable rule of decision, consistent with the framework and examples set forth in the preamble, that reflects FDA's explanation in that preamble that (i) the labeling requirements are not a mere minimum safety standard, but rather strike a balance between risks and benefits, and (ii) FDA's regulations permit changes in labeling without prior approval only in narrow circumstances. See *id.* at 3934-3935.*

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* While respondent argues (Br. in Opp. 8, 28) that FDA's 2006 preamble reflected a change in the agency's position, she relies solely on snippets from Federal Register notices that did not squarely address, much less discuss, the preemption question here. See 65 Fed. Reg. at 81,103 (stating that proposed *changes* to existing labeling rules would not have federalism implications); 63 Fed. Reg. 66,384 (1998) (response to comments concerning Medication Guides for "a small number of products," *id.* at 66,379); 44 Fed. Reg. at 37,437 (responding to comment that FDA should use different administrative procedures).

B. This Court Should Hold The Petition For A Writ Of Certiorari Pending The Decisions in *Riegel* and *Warner-Lambert*

Although the Vermont Supreme Court's decision is wrong, it does not warrant this Court's plenary review at this time.

1. Petitioner asserted (Reply 1) for the first time in its reply brief that the decision below conflicts with *Dowhal* v. *Smithkline Beecham Consumer Healthcare*, 88 P.3d 1 (Cal. 2004). There is no conflict. In *Dowhal*, California law required over-the-counter stop-smoking products containing nicotine to provide a specific health warning. *Id.* at 3-4. When the drug companies asked FDA for permission to change their labels to comply with the California law, FDA repeatedly denied their requests, told them to continue to use a different FDA-approved warning, and stressed that "*[a]ny additional or modified warning may render the product misbranded.*" *Id.* at 5-6. FDA was concerned that a stronger warning against the use of stop-smoking products would harm the public health by causing pregnant women to continue smoking instead of using the (less harmful) stop-smoking products. *Id.* at 4-5. Even when FDA ultimately permitted the companies to modify their warning labels, it prohibited them from using the particular labels required by the California law. *Id.* at 10-11. Against that unusual backdrop, the California Supreme Court correctly held that the state law was preempted. *Id.* at 11.

There is no square conflict because the *Dowhal* court tied its holding, not to FDA's approval of a new drug application, but to the agency's subsequent, specific prohibition of the warnings that would have complied with

California law. 88 P.3d at 10-11. On the facts of this case, in contrast, the Vermont Supreme Court determined that "FDA has not indicated that a stronger warning would be misleading." Pet. App. 13a; see *id.* at 16a-19a. While FDA had rejected alternative labeling proposed by petitioner, the court below determined that there was no indication that FDA did so "to preserve the use of IV push as a method of administering Phenergan." *Id.* at 17a. Thus, the two decisions are reconcilable based on the differing findings of fact in each case, and the Vermont Supreme Court might have found preemption in a case like *Dowhal* even under its erroneous impossibility standard of conflict preemption. To be sure, petitioner may dispute the Vermont Supreme Court's interpretation of the record in this case. And the United States submits that respondent's claims are preempted regardless of whether FDA explicitly rejected the specific warning now proposed by respondent, because the agency nonetheless balanced the relevant considerations in approving the product's labeling after being informed of the relevant risks. But those disagreements with the decision below do not amount to a conflict in legal authority.

2. Petitioner also relies (Reply 1-2) on a circuit split concerning the preemptive effect of FDA's premarket approval of Class III medical devices. That conflict is real, but is not directly implicated here because this case involves implied preemption based on FDA's approval of a new drug application and regulations governing changes in labeling, not express preemption based on FDA's premarket approval of a medical device. Cf. 21 U.S.C. 360k(a) (expressly preempting certain requirements with respect to medical devices). Most importantly, this Court already granted review in *Riegel* to determine the

preemptive scope of FDA's premarket approval of a Class III medical device, and the Court heard argument in that case on December 4, 2007.

As petitioner's reliance (Reply 1-2) on the medical-device cases reflects, there is significant overlap between the preemption question in this case and the preemption question in *Riegel*. While the FDCA contains an express preemption provision concerning devices (but not drugs), see 21 U.S.C. 360k, this Court has determined that implied preemption principles are relevant to the interpretation of that provision. See *Lohr*, 518 U.S. at 500; *id.* at 508 (Breyer, J., concurring).

Moreover, FDA's review of new drug applications and its premarket approval process for Class III devices are similar. See 60 Fed. Reg. at 39,180-39,181. In both instances, FDA conducts an extensive review of a product's safety and efficacy, balances health benefits against health risks in determining whether to grant approval, and generally precludes the manufacturer from making changes without the agency's prior approval. See U.S. Br. at 10-14, *Riegel*, *supra* (No. 06-179); pp. 8-14, *supra*. Under each regulatory regime, the manufacturer can make unilateral changes in labeling only in narrow circumstances while its supplemental application is pending with FDA. See *ibid.* Accordingly, this Court's resolution of *Riegel* is likely to be instructive on the question presented here.

In addition, the petition in *Warner-Lambert* (which the Court granted after inviting the views of the Solicitor General in this case) poses the related question whether the FDCA impliedly preempts state tort claims that require a court to determine, as a condition for imposing damages liability, whether a drug manufacturer defrauded FDA in a new drug application and whether

FDA would have denied or withdrawn approval of the drug but for that fraud. See Pet. at (i), *Warner-Lambert*, *supra*. That case differs from this one because the question there involves preemption of state-law determinations of fraud on FDA, while the question here involves preemption of common-law tort claims based on FDA's approval of a new drug application. Nonetheless, because *Warner-Lambert* involves implied preemption of claims involving FDA's approval of a new drug application, the decision in *Warner-Lambert* may also shed light on the proper resolution of the question in this case. For that reason as well, the Court should hold the petition in this FDA preemption case pending its resolution of the two FDA preemption petitions it has already granted for this Term.

CONCLUSION

The Court should hold the petition for a writ of certiorari pending its disposition of *Riegel* v. *Medtronic, Inc.*, No. 06-179 (argued Dec. 4, 2007), and *Warner-Lambert Co., LLC* v. *Kent*, cert. granted, No. 06-1498 (Sept. 25, 2007), and then dispose of the petition as appropriate in light of its disposition of those cases.

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Supreme Court of the United States

WYETH,

Petitioner,

v.

DIANA LEVINE,

Respondent.

On Petition for a Writ of Certiorari
to the Supreme Court of Vermont

BRIEF FOR THE PHARMACEUTICAL RESEARCH AND MANUFACTURERS OF AMERICA AS AMICUS CURIAE SUPPORTING PETITIONER

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QUESTION PRESENTED

Whether the prescription drug labeling judgments imposed on manufacturers by the Food and Drug Administration ("FDA") pursuant to FDA's comprehensive safety and efficacy authority under the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 301 *et seq.*, preempt state law product liability claims premised on the theory that different labeling judgments were necessary to make drugs reasonably safe for use.

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INTEREST OF AMICUS CURIAE

The Pharmaceutical Research and Manufacturers of America ("PhRMA") is a voluntary, nonprofit association that represents the country's leading research-based pharmaceutical and biotechnology companies.[1] PhRMA's members are dedicated to discovering medicines that enable patients to lead longer, healthier, and more productive lives. Member companies are the source of a majority of all new medicines that are discovered and marketed. In the past decade alone, PhRMA's members invested approximately $300 billion to develop new medicines. *See* PhRMA, *Pharmaceutical Industry Profile 2007* 42 (2007). New medicines accounted for 40% percent of the lifespan increase between 1986 and 2000. *See* Frank R. Lichtenberg, *The Impact of New Drug Launches on Longevity: Evidence From Longitudinal, Disease-Level Data From 52 Countries, 1982-2001* 21 (Nat'l Bureau of Econ. Research, Working Paper No. 9754, 2003).

PhRMA's members closely monitor legal issues that affect the entire industry, and PhRMA often offers its perspective in cases raising such issues. The issues in this case are especially significant. Unlike cases that address the law of an individual state, this case presents federal preemption issues that arise across the tens of thousands of product-liability lawsuits faced by PhRMA's members. When these state-law suits undermine FDA's regulation of pharmaceutical labeling, patients are deterred from using beneficial medicines and PhRMA's members are deterred from developing new ones.

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[1] Each party has consented to the filing of this brief and each party's letter of consent has been lodged with the Clerk. Pursuant to Supreme Court Rule 37.6, no party authored this brief in whole or in part, and no person or entity other than PhRMA or its members contributed money to the preparation or submission of the brief. A list of PhRMA's members is available at http://www.phrma.org.

STATEMENT

In this case, over the dissent of its Chief Justice, the Vermont Supreme Court upheld a nearly $7 million judgment against a manufacturer of an injectable medicine. The manufacturer was held liable because the medicine's labeling failed to disclaim a method of injection that FDA had expressly permitted after reviewing the drug's risks and benefits.

A. Before a new drug may be introduced into U.S. commerce, FDA must conclude that the drug is safe and effective for its proposed uses. *See* 21 U.S.C. § 355, *reprinted in* Pet. App. 84a-110a. In practice, FDA approves new drugs after a "sponsor demonstrates that their benefits outweigh their risks for a specific population and a specific use." *Examining Food and Drug Administration's (FDA) Drug Approval Process: Hearing Before the S. Comm. on Health, Education, Labor, and Pensions*, 109th Cong. 9 (2005) (joint prepared statement of Sandra L. Kweder, M.D., Deputy Dir., Office of New Drugs at Ctr. for Drug Eval. & Resrch., U.S. FDA & Janet Woodcock, M.D., FDA's Acting Deputy Comm'r for Operations).

Congress has entrusted FDA with the exclusive responsibility for making these scientific determinations. When it evaluates new drugs, "FDA considers not only complex clinical issues related to the use of the product in study populations, but also important and practical public health issues pertaining to the use of the product in day-to-day clinical practice." *Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products*, 71 Fed. Reg. 3922 (Jan. 24, 2006), *reprinted in* Pet. App. 128a-129a ("*2006 FDA Labeling Regulations*").

"Few if any drugs are completely safe in the sense that they may be taken by all persons in all circumstances without risk." *United States v. Rutherford*, 442 U.S. 544, 555 (1979). Thus, a prescription drug must bear "labeling" for physicians that, based on all available scientific information, accurately and fairly describes the drug's intended uses and potential risks. *See* 21 U.S.C. § 355(d), *reprinted in* Pet. App. 107a-108a. A drug's labeling is the "centerpiece of [its] risk management." *2006 FDA Labeling Regulations*, *reprinted in* Pet. App. 129a. The labeling "reflects thorough FDA review of the pertinent scientific evidence and communicates to health care practitioners the agency's formal, authoritative conclusions regarding the conditions under which the product can be used safely and effectively." *Id.*

Federal law prohibits the introduction into commerce of drugs that are "misbranded," and federal law grants to FDA the exclusive authority to enforce the statutory prohibition against misbranding. *See* 21 U.S.C. § 331(a), (b), (k). "Misbranding" occurs when the labeling is "false or misleading in any particular." *Id.* § 352(a).

A manufacturer may propose revisions to its FDA-approved labeling at any time and must propose revisions in certain situations. But FDA intends for revisions to reflect new information—not to revisit the agency's scientific evaluation of existing information. FDA "may later deny approval of the [revised labeling], and the labeling remains subject to enforcement action if the added information makes the labeling false or misleading." *2006 FDA Labeling Regulations*, *reprinted in* Pet. App. 130a.

Thus, "manufacturers typically consult with FDA before [revising the labeling] to avoid implementing labeling changes with which the agency ultimately might disagree (and that therefore might subject the manufacturer to en-

forcement action)." *Id.* at 132a. As explained by a former FDA Chief Counsel, "[t]he actual freedom of manufacturers unilaterally to change the packet insert is minimal." Richard M. Cooper, *Drug Labeling & Products Liability: The Role of the Food & Drug Administration*, 41 Food Drug Cosm. L.J. 233, 236 (1986).

B. State-law product-liability suits typically turn on the adequacy of the drug's FDA-approved labeling. Because no drug can be made perfectly safe, pharmaceutical manufacturers generally discharge their duties under state law if "prescribing health-care providers are adequately informed of the [drug's] relevant benefits and risks." Restatement (Third) Torts § 6 cmt. b (1998); *see also* Restatement (Second) Torts § 402A cmt. k (1965) (similar). When seeking to hold a manufacturer liable under state law, a plaintiff will argue either that the drug's labeling omitted a warning about an alleged side effect or that the drug's labeling included a statement that was affirmatively misleading.

In response to claims that their drugs' FDA-approved labeling is inadequate under state law, some defendants have argued that federal law preempts such state-law claims. Courts have considered a range of preemption arguments, which depend upon how directly FDA has considered the language at issue. Some courts have considered whether mere FDA approval of the labeling preempts state-law claims that the labeling was inadequate. *See, e.g.*, *Peters v. Astrazeneca, LP*, 417 F. Supp. 2d 1051, 1055 (W.D. Wis. 2006) (addressing whether "the FDA drug labeling process so thoroughly occupies the legislative field that it may be reasonably inferred that Congress left no room for state product liability law to supplement it") (quotations omitted). Other courts have considered whether state-law claims are preempted when FDA has considered the specific health and safety issues or warn-

ing proposal implicated by the claim at issue. *See, e.g.*, *Jackson v. Pfizer, Inc.*, 432 F. Supp. 2d. 964, 968-69 (D. Neb. 2006) (considering whether failure-to-warn claim was preempted because defendant attempted to include warning at issue and "FDA did not insert those warnings").

The claim at issue in this case implicates the latter scenario. Plaintiff received her drug through an "IV-push"—"direct intravenous injection into her arm." Pet. App. 2a. After the drug accidentally entered her artery, she suffered gangrene, and doctors were forced to amputate her hand and forearm. *See id.* At the time Plaintiff received the drug, its labeling warned physicians that arterial injection causes gangrene and requires amputation. *See id.* at 4a. The labeling also advised that it is "USUALLY PREFERABLE TO INJECT [THE DRUG] THROUGH THE TUBING OF AN INTRAVENOUS INFUSION SET." *Id.*

Before Plaintiff received her injection, Wyeth sought to enhance the existing warning about the preferred use of an intravenous infusion set over IV-push. Wyeth proposed the following warning: "INJECTION THROUGH A PROPERLY RUNNING INTRAVENOUS INFUSION MAY ENHANCE THE POSSIBILITY OF DETECTING ARTERIAL PLACEMENT." *Id.* at 4a-5a. FDA rejected Wyeth's enhanced warning and directed the company to "[r]etain [the] verbiage in [the] current label." *Id.* at 162a.

C. The arguments for preemption in this case are especially strong because Wyeth was held liable for failing to disclaim a particular method of administering the drug. FDA had expressly determined that the labeling should endorse this particular method of administration in at least some circumstances.

Notwithstanding the warning about the potential risks of direct intravenous injection, Plaintiff argued, and the jury agreed, that "the label should not have allowed IV push as a means of administration." Pet. App. 3a. Although FDA has long recognized the risks of direct intravenous injection, *see id.* at 53a, the agency has never sought to bar this method of administration. As Wyeth explains in its petition for certiorari, in some circumstances direct intravenous injection may be desirable. Direct intravenous injection delivers the drug more quickly and thus is more likely to prevent dehydration in cases of severe nausea. In addition, direct intravenous injection may be necessary to deliver the drug to patients who are overweight or to patients whose muscles receive diminished blood flow. *See* Pet. for Cert. at 8 & n.3. Moreover, FDA has long considered the risks of direct intravenous injection, and Plaintiff did not present any new information that had escaped FDA's attention.

Thus, the state-law requirement here directly contradicts an informed FDA decision about the appropriate use of the drug. Wyeth was held liable for failing to disavow an approved method of administration that FDA has determined benefits the health of at least some patients.

SUMMARY OF ARGUMENT

The Vermont Supreme Court's decision significantly affects the pharmaceutical industry and the public health, and the decision conflicts with a decision of another state's highest court. Accordingly, this Court should grant the petition for certiorari.

First, the Vermont Supreme Court's decision profoundly affects the pharmaceutical industry and the public health. Federal preemption is perhaps the single most important product-liability issue confronting PhRMA's

members. Pharmaceutical companies face an unprecedented number of state-law suits in which plaintiffs seek to revisit FDA decisions about a drug's labeling. These lawsuits encourage manufacturers to include warnings that are scientifically unsupported, discourage physicians and patients from using beneficial drugs, and deter the development of new drugs that would enhance patient health and safety. FDA itself has recognized that the public health suffers when state law imposes liability for compliance with FDA decisions.

Second, the Vermont Supreme Court's decision conflicts with a decision of the California Supreme Court. In both cases, plaintiffs sought to hold defendants liable for failing to warn against a specific use, even though FDA had approved those uses based on its scientific review of their risks and benefits. Each court based its decision on the doctrine of implied conflict preemption, and each court was asked to address both the "impossibility" and "obstacle" strands of conflict preemption. But whereas the California Supreme Court held that the plaintiffs' claims conflicted with federal law, the Vermont Supreme Court held that they did not.

ARGUMENT

I. The Vermont Supreme Court's Decision Significantly Affects The Pharmaceutical Industry And The Public Health.

This case presents legal questions that directly and significantly affect both the pharmaceutical industry and the public health. Pharmaceutical manufacturers face tens of thousands of state-law suits challenging the adequacy and truthfulness of FDA-approved labeling. Many of these lawsuits seek to hold defendants liable for failing to adopt labeling that FDA specifically rejected or for fail-

ing to deviate from warning language that FDA approved after scrutinizing the drug's safety and effectiveness. These suits threaten the public health by deterring innovation and by interfering with FDA's regulation of drug safety and efficacy.

A. An Unprecedented Number of State-Law Suits Seek to Hold Defendants Liable for Complying with FDA's Labeling Decisions.

Numerous plaintiffs seek to hold manufacturers liable under state law for adhering to warnings that FDA approved or for failing to adopt warnings that FDA rejected. Many of these lawsuits implicate the preemption defenses at issue in this case.

For example, there are currently eighteen federal multidistrict litigations in which plaintiffs challenge the adequacy or truthfulness of FDA-approved drug labeling. Twelve involve more than two-hundred plaintiffs; nine involve more than five-hundred plaintiffs; and six involve more than a thousand plaintiffs. *See* Jud. Panel on Multidistrict Litig., *Distribution of Pending MDL Dockets* (Mar. 12, 2007) ("*Pending MDL Dockets*"), *available at* http://www.jpml.uscourts.gov. "Such suits now account for more than a third of all product filings in federal courts, outnumbering asbestos, tobacco and auto safety claims by a widening margin since 2002." Lisa Girion, *State Vioxx Trial is Set as Drug Suits Boom*, L.A. Times, June 27, 2006, at C1.

State courts are equally inundated with mass-tort suits in which plaintiffs challenge the adequacy of FDA-approved labeling. For instance, eight of the thirteen consolidated actions designated as Mass Torts by the New Jersey courts involve challenges to FDA-approved labeling for prescription drugs. *See* N.J. Judiciary, *Mass Tort*

Information Center ("*NJ Mass Torts*"), *at* http://www.judiciary.state.nj (last visited Apr. 19, 2007). Several of these suits involve hundreds of plaintiffs, and two involve thousands. *See id.*

Challenges to FDA-approved labeling affect the entire industry and target entire classes of medicines. For example, Bristol-Myers Squibb faces multiple product-liability suits in connection with at least two of its FDA-approved medicines; Merck and Novartis in connection with at least three; Pfizer and GlaxoSmithKline in connection with at least five; and Wyeth in connection with at least six.[2] FDA-approved labeling is at issue in litigation over at least seven different antidepressants, at least three different antipsychotic medications, at least four different types of diet drugs, several different hormone-replacement therapies, and an additive used in multiple vaccines.[3] Collectively, these suits will cost individual companies billions of dollars. *See, e.g.*, Karen Gullo & Margaret Cronin Fisk, *Drug Maker Faces Thousands of*

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[2] *See* Bristol-Myers Squibb Co., Annual Report (Form 10-K), at 136 (Feb. 26, 2007); Merck & Co., Annual Report (Form 10-K)), at 22, 29, 31 (Feb. 28, 2007); Novartis AG, Registration of Securities of Foreign Private Issuers (Form 20-F), at F-54-55 (Jan. 31, 2007); Pfizer Inc., Annual Report (Form 10-K) (Mar. 1, 2007), Ex. 13 at 68-71; GlaxoSmithKline PLC, Registration of Securities of Foreign Issuers (Form 20-F), at 159-60 (Mar. 2, 2007); Wyeth, Annual Report (Form 10-K), at 43-46 (Feb. 26, 2007).

[3] *See Pending MDL Dockets*, *supra* (antidepressants Serzone, Paxil, Celexa, Lexapro; diet drugs Meridia, Phentermine, Fenfluramine, and Dexfenfluramine; and hormone-replacement therapy Prempro); *NJ Mass Torts*, *supra* (anti-psychotic drugs Risperdal, Seroquel, and Zyprexa; and synthetic hormones manufactured by "several pharmaceutical companies"); *Sykes v. Glaxo-SmithKline*, – F. Supp. 2d – , 2007 WL 957337 (E.D. Pa. Mar. 28, 2007) (thimerosal); *Jackson v. Pfizer*, 432 F. Supp. 2d 964 (D. Neb. 2006) (antidepressants Zoloft and Efexor); *Lasure-Radke v. Par Pharm., Inc.*, 426 F. Supp. 2d 1163 (W.D. Wash. 2006) (antidepressant fluoxetine).

New Claims, Int'l Herald Trib., Apr. 21, 2006, at 19 (Eli Lilly has reserved $1 billion for Zyprexa lawsuits); Pfizer Inc., Annual Report (Form 10-K) (Mar. 1, 2007), Ex. 13 at 68 (in 2003, Pfizer spent $975 million on Rezulin lawsuits); Merck & Co., Annual Report (Form 10-K)), at 28-29 (Feb. 28, 2007) (Merck has reserved $858 million for Vioxx lawsuits).

These suits are so prevalent and their results so unpredictable that many pharmaceutical companies are unable to implement basic safeguards against catastrophic financial harm. "[M]ost pharmaceutical companies have extreme difficulty obtaining basic insurance coverage in the traditional liability insurance market." Rochelle Chodock, et al., *"Insuring" The Continued Solvency of Pharmaceutical Companies in the Face of Product Liability Class Actions*, 40 Tort Trial & Ins. Prac. L.J. 997, 1000 (2005). Insurance experts have observed that "the pharmaceutical industry presents one of the most volatile risk management challenges in the world of business today." Mindy W. Toran, *Industry Risk Report: The Life Sciences*, Risk & Ins., Dec. 2003, at 1.

Manufacturers' inability to obtain the basic financial safeguard of insurance demonstrates that state-law actions present an intolerable level of risk. The insurance industry has literally determined that the risk associated with these lawsuits is so volatile and unpredictable that it cannot be measured or managed.

Preemption questions like the one at issue in *Levine* often determine the scope and viability of these individual and mass tort suits. *See, e.g.*, *In re Aredia & Zometa Prods. Liab. Litig.*, No. 3:06-MD-1760, 2007 WL 649266, at *4 (M.D. Tenn. Feb. 27, 2007) (discussing potential preemption defenses); *In re Zyprexa Prods. Liab. Litig.*, 238 F.R.D. 539, 539-40 (E.D.N.Y. 2006) (requesting sup-

plemental briefing on FDA preemption). For example, in many cases plaintiffs seek to hold defendants liable for declining to adopt warnings that FDA specifically rejected. *See, e.g.*, *Jackson*, 432 F. Supp. 2d at 968 (rejecting defendant's preemption argument even though FDA rejected warning at issue); *Colacicco v. Apotex, Inc.*, 432 F. Supp. 2d 514, 527-28 (E.D. Pa. 2006) (accepting defendant's preemption argument because FDA rejected warning at issue), *appeal docketed*, No. 06-3107 (3d Cir. June 21, 2006). In these cases, the defendant can avoid liability only by violating federal law and subjecting itself to federal penalties for misbranding.

B. These Lawsuits Harm The Public Health.

While ostensibly motivated by concern for patients' safety, the proliferation of state-law challenges to FDA-approved labeling actually harms the public health. "State actions are not characterized by centralized expert evaluation of drug regulatory issues. Instead, they encourage, and in fact require, lay judges and juries to second-guess the assessment of benefits versus risks of a specific drug to the general public—the central role of FDA—sometimes on behalf of a single individual or group of individuals." *2006 FDA Labeling Regulations*, *reprinted in* Pet. App. 134a. The resulting distortion of risk-benefit assessment drives beneficial drugs from the market, distracts FDA from promoting health and safety, and produces labeling that is inaccurate and confusing.

1. State-law actions like *Levine* may force valuable drugs from the market and stifle the development of new ones. "Tort litigation may drive from the market not just individual manufacturers of multi-source drugs but also entire product lines." Lars Noah, *Triage in the Nation's Medicine Cabinet: The Puzzling Scarcity of Vaccines and Other Drugs*, 54 S.C. L. Rev. 371, 392 (2002).

The scholarly literature supplies several examples:

- **Vaccines:** "Liability hazards led many firms to exit the vaccine market." W. Kip Viscusi, *Corporate Risk Analysis: A Reckless Act?*, 52 Stan. L. Rev. 547, 583 (2000). The result has been "recent shortages of five routinely recommended childhood vaccines, and the well-publicized annual shortages of the influenza vaccine." Elissa Levy, Note, *The Health Act's FDA Defense to Punitive Damages: A Gift to Drug Makers or to the Public?*, 74 Fordham L. Rev. 2425, 2447 (2006).

- **Contraceptives:** "Pharmaceutical companies have moved out of contraceptive research because of fear of product liability lawsuits. . . ." William M. Brown, *Déjà Vu All Over Again: The Exodus from Contraceptive Research and How to Reverse It*, 40 Brandeis L.J. 1, 32 (2001).

- **Drugs for Rare Diseases:** "[L]iability concerns serve to deter treatment of persons with rare diseases, delay development of drugs, and increase insurance costs." Gregory C. Jackson, *Pharmaceutical Product Liability May Be Hazardous to Your Health: A No-Fault Alternative to Concurrent Regulation*, 42 Am. U. L. Rev. 199, 208 n.61 (1992).

The litigation-induced demise of the morning-sickness drug Bendectin is illustrative. Questionable scientific theories drove the litigation and ultimately informed this Court's landmark ruling in *Daubert v. Merrell Dow Pharmaceuticals, Inc.*, 509 U.S. 579 (1993). Along the way, the manufacturer "voluntarily withdrew Bendectin from the market, citing an increasing number of lawsuits and declining sales due to negative publicity." Joseph Sanders, *From Science to Evidence: The Testi-*

mony on Causation in the Bendectin Cases, 46 Stan. L. Rev. 1, 7 (1993). No comparable drug has replaced it.

Experts have since discredited the purported connection to birth defects that drove Bendectin from the market: "[S]tudies clearly demonstrate that Bendectin has no measurable reproductive risks to the mother or the fetus." Robert Brent, *Medical, Social, and Legal Implications of Treating Nausea and Vomiting of Pregnancy*, 186 Am. J. Obstetrics & Gynecology S262, S262-63 (2002). Because untreated morning sickness can cause dehydration, Bendectin's absence has actually increased threats to fetal health. *See id.* at S264 (treatment of severe morning sickness improves "nutrition for mother and fetus" and "decrease[s] risk of some pregnancy complications").

2. Decisions like the Vermont Supreme Court's will encourage companies to "submit a deluge of information that [FDA] neither wants nor needs." *Buckman Co. v. Plaintiffs' Legal Comm.*, 531 U.S. 341, 351 (2001). This consequence, which partly motivated the Court's recent FDA-preemption holding in *Buckman*, will distract FDA officials from their core responsibilities of protecting health and safety.

Levine will actually impose greater burdens than contemplated in *Buckman*. Whereas the Court in *Buckman* preempted state-law claims based on a concern that they would encourage companies to burden FDA with excessive information, the *Levine* decision encourages companies to burden FDA with unscientific proposals for labeling changes. Unnecessary proposals for labeling changes will interfere with FDA's operations more than will mere submissions of information: whereas the agency may respond to excess information as it deems fit, it *must* respond to actual proposals.

Moreover, in denying any weight to FDA's rejection of Wyeth's attempt to strengthen the labeling, the court refused to "interpret the FDA's statement as evidence that it would have rejected *any* attempt by defendant to strengthen its label." Pet. App. 17a (emphasis added). This hairsplitting encourages manufacturers to inundate FDA with repeated and duplicative for labeling changes that FDA has already rejected in substance. Such duplicative requests will further distract FDA scientists from policing drug safety. They will also raise the already "high costs of regulatory approval and compliance [that] deter even large, well-financed drug and medical device companies from investing in research and development." Charles J. Walsh, *Rationalizing the Regulation of Prescription Drugs & Medical Devices: Perspectives on Private Certification & Tort Reform*, 48 Rutgers L. Rev. 883, 931 (1996).

3. Regulatory bottlenecks aside, FDA has long recognized that "it would be inappropriate to require statements in drug labeling that do not contribute to the safe and effective use of the drug, but instead are intended solely to influence civil litigation in which the agency has no part." *Content and Format for Labeling of Human Prescription Drugs*, 44 Fed. Reg. 37434, 37435 (June 26, 1979). Yet decisions like *Levine* encourage manufacturers to base warnings on litigation risk rather than on science.

Unnecessary warnings deter doctors and patients from using beneficial drugs. "[T]he risk of harm may be so remote that it is outweighed by the greater risk that a warning will scare consumers into foregoing use of a product that in most cases will be to their benefit." *Dowhal v. SmithKline Beecham Consumers Healthcare*, 88 P.3d 1, 14 (Cal. 2004).

Extra warnings also obscure existing ones. According to a bipartisan group of former FDA Chief Counsels, state-imposed warnings erode "FDA's ability to advance the public health by allocating scarce space in product labeling to the most important information." 150 Cong. Rec. S8,657 (July 22, 2004). Ultimately, "[w]arnings about dangers with less basis in science or fewer hazards could take attention away from those that present confirmed, higher risks." *Brooks v. Howmedica, Inc.*, 273 F.3d 785, 796 (8th Cir. 2001).

These effects are more than hypothetical. During the 1990s, FDA conducted "two initial focus groups and a national physician survey." *Requirements for Prescription Drug Product Labels*, 65 Fed. Reg. 81082, 81083 (Dec. 22, 2000). Physicians lamented "the lack of ease in locating specific information among the extensive information presented," and they complained that "labeling overly stresses the occurrence of extremely rare events." *Id.* at 81084. Rulings like *Levine* will make risk-related information even muddier.

C. FDA Has Recognized These Threats to the Public Health.

FDA itself recognizes that the public health suffers when state law undermines the agency's regulation of prescription drug labeling. The agency has attempted to address this concern, albeit with limited success.

In 2000, upon proposing new regulations designed to make drug warnings clearer, FDA observed that "the use of labeling in product liability and medical malpractice lawsuits, together with increasing litigation costs, has caused manufacturers to become more cautious and include virtually all known adverse event information, re-

gardless of its importance or its plausible relationship to the drug." *Id.* at 81083.

In January 2006, in the preamble to its final labeling regulations, FDA identified specific ways in which state-law requirements can undermine federal goals. First, "they can erode and disrupt the careful and truthful representation of benefits and risks that prescribers need to make appropriate judgments about drug use." *2006 FDA Labeling Regulations, reprinted in* Pet. App. 133a. Second, they can "pressure . . . manufacturers to expand labeling warnings to include speculative risks and, thus, to limit physician appreciation of potentially far more significant contraindications and side effects." *Id.* Third, they can "discourag[e] safe and effective use of approved products or encourag[e] inappropriate use." *Id.*

FDA has also identified "several instances in which product liability lawsuits have directly threatened the agency's ability to regulate manufacturer dissemination of risk information for prescription drugs." *Id.* at 130a. Thus, the agency has urged courts nationwide to dismiss, on grounds of federal preemption, certain state-law claims that directly undermine the agency's ability to protect public health.[4] In many of its briefs, FDA has observed that the plaintiffs, like the plaintiff here, sought to hold

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[4] *See, e.g.*, Brief for United States as Amicus Curiae Supporting Appellees at 1, *Colacicco v. Apotex, Inc.*, No. 06-3107 (3d Cir. Dec. 4, 2006) (arguing that federal law should preempt claim, given FDA's conclusion "that the existing scientific knowledge did not support such a warning"); Brief for United States as Amicus Curiae Supporting Appellee & Cross-Appellant at 1, *Motus v. Pfizer, Inc.*, 358 F.3d 659 (9th Cir. 2004) (Nos. 02-55372/55498) (same, given FDA's "determination that there is no scientific basis for such warning"); Brief for United States as Amicus Curiae Supporting Defendant at 2, *Kallas v. Pfizer, Inc.*, No. 2:04cv0998 PGC (D. Utah Sept. 15, 2005) (same, given that desired labeling "would have misbranded the drug").

defendants liable under state law for failing to include a warning that FDA had rejected.

II. The Vermont Supreme Court's Decision Conflicts With A Decision Of The California Supreme Court.

The Vermont Supreme Court's decision exacerbates the public-health concerns discussed above and reflects the wider legal debate about whether and when state-law suits may revisit FDA's scientific judgments about pharmaceutical labeling. In this regard, the decision conflicts with a decision from the California Supreme Court and presents an excellent vehicle for this Court to clarify the scope of FDA preemption and preserve FDA's ability to protect the public health.

A. The Vermont Supreme Court's decision conflicts with the California Supreme Court's decision in *Dowhal v. SmithKline Beecham Consumer Healthcare*, 88 P.3d 1 (Cal. 2004). Although *Dowhal* involved an over-the-counter drug, in both *Levine* and *Dowhal* the plaintiffs sought to hold the defendant liable for failing to warn against an FDA-approved use of a pharmaceutical. Moreover, in both *Levine* and *Dowhal* the courts based their decisions on the doctrine of implied conflict preemption. Whereas the Vermont Supreme Court dismissed FDA's scientific judgment and allowed the claim to proceed, the California Supreme Court deferred to FDA's scientific views and held that the claim was preempted.

In *Levine*, the defendant was held liable for failing to warn physicians that the drug should not be directly intravenously injected into patients. The court rejected Wyeth's argument that inclusion of the state-law warning would have violated federal law. FDA, the court acknowledged, had not restricted the method by which the drug

could be injected and had specifically rejected Wyeth's attempt to strengthen the warning about the risks of direct intravenous injection. *See* Pet. App. 54a-55a. But the court did not defer to FDA's scientific judgment and instead asserted that Wyeth "could have warned against [direct intravenous] administration without prior FDA approval." *Id.* at 6a.

The court also rejected Wyeth's argument that state-law liability in this case would pose an obstacle to the fulfillment of federal regulatory objectives. Pointing to federal statutory language that forecloses preemption absent a "direct and positive conflict between [federal law] and state law," the court held that this language "essentially removes from our consideration the question of whether common-law tort claims present an obstacle to the purposes and objectives of Congress." *Id.* at 21a.

In reaching the opposite conclusion in *Dowhal*, the California Supreme Court respected FDA's determinations. The court addressed a preemption challenge to a state law (1) providing that the defendant's product, an over-the-counter nicotine patch, was "not for use by pregnant women," and (2) requiring the defendant to warn patients that the product "contains nicotine, a chemical known to the state of California to cause reproductive harm." 88 P.3d at 3-4. As did the court in *Levine*, the court in *Dowhal* based its decision on the doctrine of "conflict preemption." *Id.* at 7.

Like the court in *Levine*, the court in *Dowhal* acknowledged that manufacturers may, in certain circumstances, change their FDA-approved labeling without prior FDA approval (but subject to FDA approval or disapproval after the change). Unlike the court in *Levine*, however, the court in *Dowhal* acknowledged the importance of FDA's prior scientific decision: "FDA had re-

jected plaintiff's claim that his data justify a different warning, and defendants do not claim to have any additional data." *Id.* at 9.

The court in *Dowhal* also held that the state-law requirement was preempted because it would pose an obstacle to FDA's health-related objectives by deterring pregnant women from using the patch to quit smoking. *See id.* at 4 ("[T]he purpose of the products is to help individuals stop smoking, and smoking is even more dangerous to the fetus."). Unlike the Vermont Supreme Court, the California Supreme Court held that the federal statute's limitation on preemption did not foreclose preemption "if state law stands as an obstacle to the accomplishment and execution of the full purposes and objectives of Congress." *Id.* at 11 (quotations omitted).[5]

B. This case presents an ideal vehicle for this Court to alleviate the judicial conflict over FDA preemption and curb the ability of state law to undermine FDA's regulation of health and safety. *Levine* comes to the Court after a final judgment—a significant feat, given the pressure on pharmaceutical defendants to settle high-stakes personal-injury suits. *See* David E. Bernstein, *The Breast Implant Fiasco*, 87 Cal. L. Rev. 457, 493 (1999) ("[I]f a defendant loses just one major lawsuit, . . . that loss can stimulate an avalanche of copycat lawsuits.").

Moreover, in addressing the dissent's arguments, the Vermont Supreme Court recognized that courts continue

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[5] The non-prescription-labeling provision at issue in *Dowhal* exempted, from an express-preemption provision, any "State requirement adopted by a State public initiative or referendum enacted prior to September 1, 1997." 21 U.S.C. § 379r(d)(2). California's requirement was adopted by referendum in 1986 and was thus immune from express preemption. *See Dowhal*, 88 P.3d at 3.

to disagree about whether states may second-guess express FDA judgments about the uses and labeling of pharmaceuticals:

> We recognize that our dissenting colleague has reached the opposite conclusion. There is little to say, beyond what we have already said, except that we respectfully disagree with his analysis . . . . While the dissent cites favorably the minority view, we agree with the majority view.

Pet. App. 23a. These disagreements persist, moreover, even though FDA has repeatedly asked courts to foreclose state-law suits in which plaintiffs seek to revisit the agency's scientific decisions. Only this Court can reconcile these conflicting views.

CONCLUSION

PhRMA respectfully requests that the Court grant the petition.

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In the Supreme Court of the United States

WYETH,

Petitioner,

v.

DIANA LEVINE

Respondent.

On Petition for a Writ of Certiorari to the Vermont Supreme Court

BRIEF OF *AMICI CURIAE* PRODUCT LIABILITY ADVISORY COUNCIL, INC. AND U.S. CHAMBER OF COMMERCE IN SUPPORT OF PETITIONER

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BRIEF OF PRODUCT LIABILITY ADVISORY COUNCIL, INC. AND U.S. CHAMBER OF COMMERCE AS *AMICI CURIAE* IN SUPPORT OF PETITIONER

INTEREST OF THE *AMICI CURIAE*

Product Liability Advisory Council, Inc. ("PLAC") is a non-profit association with 125 corporate members representing a broad cross-section of American and international product manufacturers. These companies seek to contribute to the improvement and reform of the law in the United States and elsewhere, with emphasis on the law governing the liability of manufacturers of products. PLAC's perspective is derived from the experiences of a corporate membership that spans a diverse group of industries in various facets of the manufacturing sector. Since 1983, PLAC has filed over 725 briefs as *amicus curiae* in both state and federal courts, including this Court, presenting the broad perspective of product manufacturers seeking fairness and balance in the application and development of the law as it affects product liability. Appendix A lists PLAC's corporate members.

The Chamber of Commerce of the United States of America ("Chamber") is the world's largest business federation. The Chamber represents an underlying membership of more than three million companies and professional organizations of every size, in every industry sector, and from every region of the country. An important function of the Chamber is to represent the interests of its members in matters before Congress, the Executive Branch, and the courts. To that end, the Chamber regularly files *amicus* briefs in cases that raise issues of vital concern to the nation's business community.[1]

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[1] Pursuant to Rule 37.6, *amici* affirm that no counsel for a party authored this brief in whole or in part and that no person other than *amici* and their counsel made a monetary contribution to its preparation or submission. The parties' letters consenting to the filing of this brief have been filed with the Clerk's office.

PLAC and the Chamber—which have filed *amicus* briefs in prior preemption cases, including *Geier* v. *American Honda Motor Co.*, 529 U.S. 861 (2000), and *United States* v. *Locke*, 529 U.S. 89 (2000)—are well situated to address the issue of preemption raised in this case. Their members are engaged in commerce in each of the 50 states and are subject in varying degrees to a wide range of federal regulations. As a result, their members often confront the interplay between the duties imposed by federal law and the state common-law standards applied in product liability cases. Therefore, they not only are uniquely suited to offer a broader perspective on preemption than the parties may provide, but also are keenly interested in ensuring that the regulatory environment in which their members operate is a rational and consistent one.

INTRODUCTION AND SUMMARY OF ARGUMENT

Although this case arises in the context of federal drug regulation, its significance extends far beyond the pharmaceutical industry. If the decision below is allowed to stand, all manufacturers of federally regulated products, regardless of industry, will be at risk of having to choose between complying with federal law or complying with state law. If they decide to comply with federal law, they will—like the petitioner in this case—be exposed to multimillion dollar state-law tort liability. No company should be forced to make that choice or to suffer those consequences.

In addition to being fundamentally unfair, the decision below impedes interstate commerce and threatens the proper functioning of the federal regulatory system. In allowing private litigants to hold manufacturers liable under state law for failing to include risk warnings that are contrary to those mandated by the relevant federal agency, the Vermont Supreme Court—expressly disregarding the agency's views—misconstrued federal statutes and misapplied this Court's precedent. The results are potentially devastating. Permitting juries in individual cases to substitute their *ad hoc* conclusions for those reached by an expert federal agency can easily

upset the delicate regulatory balance struck by that agency after comprehensive review and careful consideration of all available scientific information.

Unfortunately, the Vermont Supreme Court is not alone in its error. Although some courts have correctly concluded that approval of a drug label by the Food and Drug Administration preempts state-law failure-to-warn claims, many others have reached the opposite, erroneous conclusion. Like the court below, they have failed to give due deference to the FDA's authoritative interpretation of the Food, Drug and Cosmetic Act ("FDCA"). As a result, the public health has been endangered and the goal of national uniformity in drug regulation has been undermined.

It is vitally important that this Court grant certiorari to vindicate the Supremacy Clause and to resolve the dangerous split in lower court authority.

ARGUMENT

I. The Decision Below Thwarts Important Federal Policy By Erroneously Denying Preemptive Effect To The FDA's Approval Of Petitioner's Drug Label.

The FDA is the expert federal agency charged by Congress with ensuring that drugs are safe and effective. To that end, the FDCA mandates that drug manufacturers obtain FDA approval to market prescription drugs. The agency decides whether to approve a drug based "on a comprehensive scientific evaluation of the product's risks and benefits under the conditions of use prescribed, recommended, or suggested *in the labeling*." Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products, 71 Fed. Reg. 3922, 3934 (Jan. 24, 2006) ("Preemption Preamble") (citing 21 U.S.C. § 355(d)) (emphasis added). Indeed,

> [t]he *centerpiece* of risk management for prescription drugs generally is the labeling which reflects thorough FDA review of the pertinent scientific evi-

> dence and communicates to health care practitioners the agency's formal, authoritative conclusions regarding the conditions under which the product can be used safely and effectively. FDA carefully controls the content of labeling for a prescription drug, because such *labeling is FDA's principal tool for educating health care professionals about the risks and benefits of the approved product to help ensure safe and effective use.*

Ibid. (emphasis added); see also *id.* at 3967–3969; New Drug and Antibiotic Regulations, 50 Fed. Reg. 7452, 7470 (Feb. 22, 1985) ("Drug labeling serves as the standard under which FDA determines whether a product is safe and effective."). By imposing state-law tort liability on a drug manufacturer despite the manufacturer's compliance with FDA labeling directives, the decision below "threaten[s] FDA's statutorily prescribed role as the expert Federal agency responsible for evaluating and regulating drugs." 71 Fed. Reg. at 3935.

A. State-law failure-to-warn liability conflicts with the FDA's goals of preventing overwarning and patchwork regulation.

The FDA's overarching goal in regulating the warning labels of pharmaceuticals is to strike the right balance between providing sufficient information to drug users and providing too many, or the wrong kind of, warnings. "FDA seeks to encourage the optimal level of use in light of reasonable safety concerns, by requiring scientific evidence of an association between a drug and a particular hazard before warning of that association on a drug's labeling." Brief for *Amicus Curiae* the United States of America at 14, *Colacicco* v. *Apotex, Inc.*, 432 F. Supp. 2d 514 (E.D. Pa. 2006) (No. 05-CV-05500-MMB), 2006 WL 1724170 (citing 21 C.F.R. § 201.57(e)) ("FDA *Colacicco* Br."). To achieve that goal, "FDA considers not only complex clinical issues related to the use of the product in study populations, but also important and practical public health issues pertaining to use of the

product in day-to-day clinical practice." 71 Fed. Reg. at 3968. Through careful consideration of these factors, "appropriate warnings are drafted that identify established risks while avoiding inadequately substantiated risks, mention of which could improperly deter use of the drug to the detriment of the very patients it is designed to benefit." FDA *Colacicco* Br. 5.

In the Preemption Preamble, the FDA emphasized how delicate and important this balance is, and how overwarning can harm patients and interfere with regulatory goals:

> Given the comprehensiveness of FDA regulation of drug safety, effectiveness, and labeling under the act, additional requirements for the disclosure of risk information are not necessarily more protective of patients. Instead, they can erode and disrupt the careful and truthful representation of benefits and risks that prescribers need to make appropriate judgments about drug use.

71 Fed. Reg. at 3935; *accord* FDA *Colacicco* Br. at 13 ("In considering the agency's views on drug labeling, it is critical to understand that, where warnings are concerned, more is not always better."). Among other dangers, "[e]xaggeration of risk could discourage appropriate use of a beneficial drug." 71 Fed. Reg. at 3935. Moreover, "labeling that includes theoretical hazards not well-grounded in scientific evidence can cause meaningful risk information to 'lose its significance.'" *Ibid.* (quoting 44 Fed. Reg. 37,434, 37,447 (June 26, 1979)). Thus, "State-law attempts to impose additional warnings can lead to labeling that does not accurately portray a product's risks, thereby potentially discouraging safe and effective use of approved products or encouraging inappropriate use and undermining the objectives of the act." *Ibid.*; see also, *e.g.*, Brief for *Amicus Curiae* the United States of America at 23–24, *Motus* v. *Pfizer, Inc.*, 358 F.3d 659 (9th Cir. 2004) (Nos. 02-55372 & 02-55498), 2002 WL 32303084 (explaining that "[u]nder-utilization of a drug

based on dissemination of scientifically unsubstantiated warnings, so as to deprive patients of beneficial, possibly lifesaving treatment, could well frustrate the purposes of federal regulation as much as over-utilization resulting from a failure to disclose a drug's scientifically demonstrable adverse effects").[2]

These concerns were echoed not long ago in a letter entered in the *Congressional Record* from five former Chief Counsel of the FDA, whose tenures date back to 1972. That letter debunked allegations that the FDA had gone "'in a radical new direction'" by arguing in its *amicus* brief in *Motus* that failure-to-warn claims are preempted by the FDCA. 150 Cong. Rec. S8657 (daily ed. July 22, 2004) (quoting 150 Cong. Rec. H5598-5599 (July 13, 2004)); *accord* 150 Cong. Rec. E1505 (July 22, 2004). These former FDA Chief Counsel, who served in both Republican and Democratic administrations, explained that, in arguing for preemption, the

[2] The briefs filed by the FDA in *Colacicco* and *Motus* are just two of the numerous *amicus* briefs supporting implied preemption filed by the FDA since 2000. In each case in which it has filed an *amicus* brief, the FDA was concerned about some aspect of civil litigation that posed a specific threat to its authority. See, *e.g.*, Corrected *Amicus* Brief for the United States, *Kallas* v. *Pfizer, Inc.*, No. 2:04CV0998 PGC (N.J. Sup. Ct. 2005), 2005 WL 4030146 (arguing that failure-to-warn claim was preempted by FDA rejection of scientific basis for warning); *Amicus Curiae* Brief of the United States of America, *Dowhal* v. *SmithKline Beecham Consumer Healthcare, LP*, 56 P.3d 1027 (Cal. 2003) (No. A094460), 2003 WL 23527781 (state-mandated statement on smoking cessation product preempted where FDA had concluded that statement should not appear); *Amicus Curiae* Brief of the United States, *In re Paxil Litig.*, No. CV 01-07937 MRP (C.D. Cal. Sept. 5, 2002) (state-law injunction against FDA-approved advertising preempted); Statement of Interest of the United States, *Bernhardt* v. *Pfizer, Inc.*, 2000 WL 1738645 (S.D.N.Y. Nov. 22, 2000) (No. 00 Civ. 4042 LLM) (state-law injunctive relief to force changes in drug labeling and issuance of "Dear Doctor" letters preempted).

"amicus curiae briefs filed by [the United States] * * * protect FDA's jurisdiction and the integrity of the federal regulatory process" because, "[i]f every state judge and jury could fashion their own labeling requirements for drugs and medical devices, there would be regulatory chaos for these two industries that are so vital to the public health, and FDA's ability to advance the public health by allocating scarce space in product labeling to the most important information would be seriously eroded." 150 Cong. Rec. S8657.

Courts and commentators alike have acknowledged the wisdom of preserving FDA primacy in reviewing and approving labeling for products over which it has regulatory authority. When the Third Circuit held in *Horn* v. *Thoratec Corp.*, 376 F.3d 163 (3d Cir. 2004), that the FDA's premarket approval process for medical devices preempts state common law claims alleging defective design and manufacture, the court relied upon the agency's conclusion that "'State common law tort actions threaten the statutory framework for the regulation of medical devices, *particularly with regard to FDA's review and approval of product labeling.*'" *Id.* at 178 (quoting the Letter Brief of *Amicus Curiae* the United States of America at 25) (emphasis added). Similarly, in *Brooks* v. *Howmedica, Inc.*, 273 F.3d 785 (8th Cir. 2001) (en banc), *cert. denied*, 535 U.S. 1056 (2002)—a failure-to-warn case involving the labeling of a medical device approved by the FDA—the Eighth Circuit identified

> a number of sound reasons why the FDA may prefer to limit warnings on product labels. Warnings about dangers with less basis in science or fewer hazards could take attention away from those that present confirmed, higher risks. A label with many varied warnings may not deliver the desired information to users. Space on product labeling material is also a factor, and the most effective labels are those with large, bold warnings and a simple design.

Id. at 796.

None of these concerns is likely, however, to motivate—or even be considered by—a jury that is asked to decide a state failure-to-warn claim. All that such a jury would be called upon to determine is whether the content of the defendant's label satisfied the defendant's state-law duty to warn of the *particular* risk encountered by the *particular* plaintiff. If the jury answers that question in the negative, liability is almost certain to attach, regardless of the potential impact that the addition of that warning might have on *other* warnings with respect to other risks or on *other* patients' ability or willingness to use the product.

This problem is exacerbated by the case-by-case process of common-law adjudication. Later judges or juries cannot reconsider outcomes reached in earlier cases. Thus, a trier of fact cannot deem unnecessary or inappropriate a warning added in response to an earlier verdict. Nor do judges and juries know how many warnings will be vying for limited reader attention.

That is precisely the role of the FDA. As the Eighth Circuit has emphasized, "[i]t would be difficult for a jury focused on a single case to take into account 'the cumulative, systemic effects' of a series of verdicts. In contrast, the FDA possesses a broader perspective." *Brooks*, 273 F.3d at 797 (quoting Richard B. Stewart, *Regulatory Compliance Preclusion of Tort Liability: Limiting the Dual-Track System*, 88 GEO. L.J. 2167, 2175 (2000)). Even where a judge or jury is aware of potential overwarning, it can do little to prevent the problem. *See* James A. Henderson, Jr. & Aaron D. Twerski, *Doctrinal Collapse in Products Liability: The Empty Shell of Failure to Warn*, 65 N.Y.U. L. REV. 265, 302 (1990).

In light of these widely recognized dangers, the FDA has reasonably determined that state-law "product liability lawsuits have directly threatened the agency's ability to regulate manufacturer dissemination of risk information for prescription drugs in accordance with the act." 71 Fed. Reg. at 3934. As the agency summarized in the Preemption Preamble:

> State actions are not characterized by centralized expert evaluation of drug regulatory issues. Instead, they encourage, and in fact require, lay judges and juries to second-guess the assessment of benefits versus risks of a specific drug to the general public— the central role of FDA—sometimes on behalf of a single individual or group of individuals. That individualized reevaluation of the benefits and risks of a product can result in relief—including the threat of significant damage awards or penalties—that creates pressure on manufacturers to attempt to add warnings that FDA has neither approved nor found to be scientifically required. This could encourage manufacturers to propose "defensive labeling" to avoid State liability, which, if implemented, could result in scientifically unsubstantiated warnings and underutilization of beneficial treatments.

Id. at 3935. Only comprehensive, exclusive regulation by an expert agency, such as the FDA, can solve the problem of overwarning by permitting an overall evaluation of risk and a rational decision about what risks are sufficiently serious to warrant inclusion on a label, how those warnings should be phrased, and where they should be placed. This is especially true where, as here, the intended readership consists not of ordinary consumers, but, under the learned-intermediary doctrine, highly trained physicians who make judgments based on scientific data and information.

In addition to the danger of overwarning created when states require warnings not approved by the FDA, state regulation via failure-to-warn claims clashes with "the need for national uniformity in product regulation." *Brooks*, 273 F.3d at 797. As the FDA has noted, if judgments under state law were allowed to trump the FDA's assessment of what may appear in drug advertisements, "the public undoubtedly would receive inconsistent information from region to region." *Amicus Curiae* Brief of the United States at 5, *In re*

Paxil Litig., 2002 WL 31375497 (C.D. Cal. Sept. 5, 2002) (No. CV 01-07937 MRP).

This Court has likewise recognized in the context of another federal labeling regime—the Federal Cigarette Labeling and Advertising Act of 1965—that the national economy can be greatly burdened if manufacturers of a product sold around the country are subjected to "diverse, nonuniform, and confusing * * * labeling and advertising regulations." *Cipollone* v. *Liggett Group, Inc.*, 505 U.S. 504, 514 (1992). Congress, in the legislative history of the Medical Device Amendments to the FDCA ("MDA"), observed that, "if a substantial number of differing requirements applicable to a medical device are imposed by jurisdictions other than the Federal government, interstate commerce would be unduly burdened." H.R. REP. NO. 853, 45 (1976) (quoted in *Brooks*, 273 F.3d at 797). For these reasons, it was reasonable for the FDA to conclude that,

> [i]f State authorities, including judges and juries applying State law, were permitted to reach conclusions about the safety and effectiveness information disseminated with respect to drugs for which FDA has already made a series of regulatory determinations based on its considerable institutional expertise and comprehensive statutory authority, the federal system for regulation of drugs would be disrupted.

71 Fed. Reg. at 3969. Not only would allowing plaintiff's claims to proceed in this case open the door to the burdening of interstate commerce in prescription drugs, but it also would set a precedent that could affect other federally-regulated industries.

B. The decision below misconstrues the FDCA and the relevant regulation promulgated thereunder.

The decision below—which expressly disregards the considered views of the FDA (see Pet. App. 26a)—rests on a fundamental misunderstanding of the FDCA and the relevant

regulation promulgated thereunder. According to the Vermont Supreme Court, plaintiff's failure-to-warn claim does not conflict "with the FDA's labeling requirements for Phenergan because defendant could have warned against IV-push administration without prior FDA approval, and because federal labeling requirements create a floor, not a ceiling, for state regulation." Pet. App. 6a. The Vermont Supreme Court is mistaken. Its decision rests on a false premise.

Contrary to what the court found, Wyeth was not at liberty to change the Phenergan label after its approval by the FDA. As the dissenting opinion explains, the applicable "regulation does not allow manufacturers to simply reassess and draw different conclusions regarding the same risks and benefits already balanced by the FDA." Pet. App. 40a. See also Pet. 19. Rather, that regulation, 21 C.F.R. § 314.70(c), permits a manufacturer to make a provisional label change *only* if there is newly discovered evidence of a previously unknown or underappreciated risk. As the FDA articulated when proposing § 314.70(c), the rule is designed to "make available important *new* information about the safe use of a drug product." New Drug and Antibiotic Regulations, 47 Fed. Reg. 46622, 46635 (proposed Oct. 19, 1982) (emphasis added). In this case, however, there was no new information. The risks associated with arterial blood exposure to Phenergan were fully known by the FDA when it approved the Phenergan label. See Pet. 6–8. Indeed, in 1997, at the conclusion of a multiyear administrative review of the Phenergan label, the FDA—with specific reference to the risk of "Inadvertent Intra-arterial Injection"—expressly directed Wyeth to "[r]etain [the] verbiage in [the] current label." Pet. App. 162a. Accordingly, Wyeth was not permitted to change the label without prior FDA approval.

As the FDA explained in the Preemption Preamble, the view (adopted by the court below) that "FDA labeling requirements represent a minimum safety standard" that may be augmented by more stringent state-law requirements is a

"misunderstanding" of the FDCA and the regulations promulgated thereunder. 71 Fed. Reg. at 3934. Because "[o]verwarning, just like underwarning, can similarly have a negative effect on patient safety and public health," requirements imposed by the FDA pursuant to the FDCA "establish both a 'floor' and a 'ceiling.'" *Id.* at 3935. Thus, contrary to the decision below, allowing state law to require an additional warning beyond those required by the FDA would "frustrate the agency's implementation of its statutory mandate." *Id.* at 3934.

It would, moreover, place manufacturers in an impossible position. If subject to state-law failure-to-warn claims, drug manufacturers will be forced to add every conceivable warning to their labels or else risk—as in this case—multimillion dollar tort liability. At the same time, however, because "the determination whether labeling revisions are necessary is, in the end, squarely and solely FDA's under the act" (71 Fed. Reg. at 3934), adding warnings to drug labels without FDA approval would expose manufacturers to administrative enforcement actions (and even criminal prosecution under 21 U.S.C. §§ 331, 333, 352).[3] In some cases, manufacturers might respond to this dilemma by withdrawing certain products from the market, thereby diminishing in-

[3] Furthermore, in what can fairly be called a Catch-22, adding warnings in response to potential tort liability might even increase a manufacturer's vulnerability to tort claims. As one commentator has suggested, "[i]t seems to be only a matter of time before a plaintiff succeeds in bringing an inadequate warning claim premised on the argument that, although a completely accurate statement of the risk had been provided, the pertinent warning lacked sufficient prominence because it was lost among the clutter of too many other cautionary statements on the label." Lars Noah, *The Imperative to Warn: Disentangling the "Right to Know" From the "Need to Know" About Consumer Product Hazards*, 11 YALE J. ON REG. 293, 379–380 (1994); see also *id.* at 380 n.435 (describing similar cases in various contexts).

terstate commerce and depriving the public of drugs that the FDA had determined to be safe and effective.

II. The Decision Below Conflicts With This Court's Precedent.

The FDA's interpretation of the FDCA is clear: Because state-law failure-to-warn tort claims interfere with the agency's expert determinations as to the proper balance to be struck in drug labels, "FDA approval of labeling under the act * * * preempts conflicting or contrary State law." 71 Fed. Reg. at 3934. In reaching the opposite conclusion, the Vermont Supreme Court acknowledged the FDA's position, but declined to give it any weight, holding that "the FDA's statement deserves no deference." Pet. App. 26a. The Vermont Supreme Court's failure to defer to the FDA's interpretation of the FDCA is contrary to this Court's precedent.

A. The decision below conflicts with this Court's decisions concerning the deference due executive agencies.

Under the Supremacy Clause of the United States Constitution, Congress may preempt state statutory or common law through federal legislation. See U.S. CONST. art. VI, cl. 2; *Chi. & N.W. Transp. Co.* v. *Kalo Brick & Tile Co.*, 450 U.S. 311, 326–327 (1981). It is well settled that federal regulations implementing such statutes "have no less pre-emptive effect than federal statutes" themselves. *Fid. Fed. Sav. & Loan Ass'n* v. *de la Cuesta*, 458 U.S. 141, 153 (1982).

In the course of delineating the circumstances in which preemption exists, this Court has held that a federal statute or regulation impliedly preempts any state law (including any state common law) that would "prevent or frustrate the accomplishment of a federal objective." *Geier*, 529 U.S. at 873–874; see also *Locke*, 529 U.S. at 109 (preemption is implied "when the state law stands as an obstacle to the accomplishment and execution of the full purposes and objective of Congress") (internal quotation marks and citation omitted).

When, as in the case of the FDA, Congress has delegated authority to an expert federal agency to implement and enforce a federal regulatory scheme, the agency's determination that state law threatens to upset federal objectives "is dispositive * * * unless either the agency's position is inconsistent with clearly expressed congressional intent, * * * or subsequent developments reveal a change in that position." *Hillsborough County* v. *Automated Med. Labs., Inc.*, 471 U.S. 707, 714–715 (1985) (citation omitted).

This deference to an agency's interpretation of the preemptive scope of a federal statute or regulation that the agency administers derives from the seminal decision in *Chevron U.S.A., Inc.* v. *Natural Resources Defense Council, Inc.*, 467 U.S. 837 (1984). As the Court explained in *Chevron*, administrative deference inheres in the congressional decision to delegate powers to the agency:

> The power of an administrative agency to administer a congressionally created * * * program necessarily requires the formulation of policy and the making of rules to fill any gap left, implicitly or explicitly, by Congress. If Congress has explicitly left a gap for the agency to fill, there is an express delegation of authority to the agency to elucidate a specific provision of the statute by regulation. Such legislative regulations are given controlling weight unless they are arbitrary, capricious, or manifestly contrary to the statute. Sometimes the legislative delegation to an agency on a particular question is implicit rather than explicit. *In such a case, a court may not substitute its own construction of a statutory provision for a reasonable interpretation made by the administrator of an agency.*

Id. at 843–844 (citations and internal quotation marks omitted; emphasis added). Thus, under *Chevron*, "a court must give effect to an agency's regulation containing a reasonable interpretation of an ambiguous statute." *Christensen* v. *Har-*

ris County, 529 U.S. 576, 586–587 (2000). That same absolute deference is accorded to "an agency's [reasonable] construction of its own regulations." *Martin* v. *Occupational Safety & Health Review Comm'n*, 499 U.S. 144, 150 (1991) (citation omitted).

In this instance, the FDA is, pursuant to the FDCA, "the expert Federal agency responsible for evaluating and regulating drugs." 71 Fed. Reg. at 3935. See also 21 U.S.C. § 393(b)(2)(B) (the FDA is to ensure that "human * * * drugs are safe and effective"). As such, it has adopted—in the Preemption Preamble and numerous *amicus* briefs (see *supra* at 1 n.2)—an authoritative interpretation of the FDCA and the agency's own regulations according to which "FDA approval of labeling under the act * * * preempts conflicting or contrary State law." 71 Fed. Reg. at 3934. That determination—based on the agency's recognition that state-law failure-to-warn claims interfere with its ability to implement finely calibrated labeling decisions under the FDCA—is reasonable, and entitled to full deference.

The fact that the FDA has articulated its preemption determination in a regulatory preamble and a series of *amicus* briefs does not diminish the deference owed that determination. As this Court recognizes, an agency's conclusion that federal law preempts state law may properly be communicated in "regulations, *preambles*, interpretive statements and responses to comments." *Hillsborough County*, 471 U.S. at 718 (emphasis added). Similarly, the fact that the "agency's fair and considered judgment on the matter in question" is conveyed "in the form of a legal brief" does not make the agency's view "unworthy of deference." *Auer* v. *Robbins*, 519 U.S. 452, 462 (1997). See also *Geier*, 529 U.S. at 883 (deferring to agency interpretation of ambiguous regulation contained in *amicus* brief submitted in dispute between private parties).

It was, therefore, contrary to this Court's precedent for the Vermont Supreme Court to disregard the FDA's authori-

tative determination that FDA approval of a drug label preempts state-law tort claims premised on the manufacturer's failure to provide a warning not required by the FDA.

B. The decision below conflicts with this Court's decisions concerning the effect of savings clauses on implied preemption.

The Vermont Supreme Court's erroneous failure to defer to the FDA's interpretation of the FDCA rests, in part, on that court's misunderstanding of this Court's preemption jurisprudence.

Recognizing that "deference to an agency's interpretation is appropriate only when a statute is 'silent or ambiguous with respect to the specific issue' the agency has considered," Pet. App. 25a (quoting *Chevron*, 467 U.S. at 842–843), the Vermont Supreme Court disregarded the FDA's interpretation of the FDCA because, in that court's opinion, (a) drug manufacturers can add warnings required by state common-law standards on their own initiative without violating federal regulations, and (b) Congress, in a savings clause, expressly limited implied preemption in the drug context to situations in which compliance with federal and state law is a physical impossibility. See Pet. App. 21a, 26a–28a. But neither premise is correct. The first rests on the court's misunderstanding of 21 C.F.R. § 314.70(c), which—contrary to the decision below—does *not* give drug manufacturers the power to add warnings unilaterally absent new, scientifically valid information. See *supra* at 11. The second rests on the court's misinterpretation of this Court's implied preemption doctrine.

Section 202 of the 1962 amendments to the FDCA provides that "[n]othing in the amendments made by this Act to the Federal Food, Drug, and Cosmetic Act shall be construed as invalidating any provision of State law * * * unless there is a direct and positive conflict between such amendments and such provision of State law." Drug Amendments of 1962 § 202, Pub. L. 87-781, 76 Stat. 780, 793 (1962). In the eyes

of the Vermont Supreme Court, this provision "remove[d] from [its] consideration the question of whether common-law tort claims present an obstacle to the purposes and objectives of Congress." Pet. App. 21a. That conclusion, however, is contrary to this Court's precedent.

As this Court made clear in *Geier*, "'conflicts' that prevent or frustrate the accomplishment of a federal objective and 'conflicts' that make it 'impossible' for private parties to comply with both state and federal law" are equally repugnant to the Supremacy Clause. 529 U.S. at 873. Accordingly, this Court has steadfastly "refused to read general 'saving' provisions"—such as Section 202—"to tolerate actual conflict *both* in cases involving impossibility *and* in 'frustration-of-purpose' cases." *Id.* at 874 (citations omitted). Because any form of conflict between federal and state law is intolerable to the Supremacy Clause, this Court rejects "attempting to distinguish among types of federal-state conflict for purposes of analyzing whether such a conflict warrants preemption in a particular case." *Ibid.*

That, however, is precisely what the Vermont Supreme Court did below. It interpreted Section 202 as abrogating state law only when simultaneous compliance with federal law is impossible, but as preserving state law even if it "present[s] an obstacle to the purposes and objectives of Congress." Pet. App. 21a. Neither the Supremacy Clause nor this Court's precedent permits such a result.[4]

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[4] Notably, the language used by Congress in Section 202 to describe which state laws are preempted—namely state laws that are in "direct and positive conflict" with federal law—is identical to that used by this Court in *Sinnot* v. *Davenport*, 63 U.S. (22 How.) 227, 243 (1859). In that case, this Court held that a state law, which imposed a registration requirement on steamboats beyond that imposed by a federal law meant to facilitate interstate transport, was preempted *even though simultaneous compliance with both state and federal law was not impossible*. Thus, *Sinnot* makes clear that the phrase "direct and positive conflict" encompasses

III. This Case Is An Appropriate Vehicle For Resolving A Recurring Conflict In The Lower Courts On An Important Issue Of Federal Statutory Interpretation.

A. Certiorari should be granted in this case.

As acknowledged by both the majority and dissenting opinions below (see Pet. App. 11a–13a; Pet. App. 23a; Pet. App. 39a n.7; see also Pet. 16–17), the lower courts are deeply divided on whether the FDCA preempts state-law tort claims alleging that an FDA-approved drug label failed to provide adequate warning. Compare, *e.g.*, *Sykes* v. *GlaxoSmithKline*, 2007 WL 957337 (E.D. Pa. Mar. 28, 2007) (notice of appeal filed Mar. 29, 2007) (holding state-law failure-to-warn claims preempted); *In re Bextra & Celebrex Mktg. Sales Practices & Prod. Liab. Litig.*, 2006 WL 2374742 (N.D. Cal. Aug. 16, 2006) (same); *Needleman* v. *Pfizer, Inc.*, 2004 WL 1773697 (N.D. Tex. Aug. 6, 2004) (same); *Dusek* v. *Pfizer Inc.*, 2004 WL 2191804 (S.D. Tex. Feb. 20, 2004) (same); *Ehlis* v. *Shire Richwood, Inc.*, 233 F. Supp. 2d 1189 (D.N.D. 2002) (same), aff'd on other grounds, 367 F.3d 1013 (8th Cir. 2004); with, *e.g.*, *Laisure-Radke* v. *Par Pharm., Inc.*, 2006 WL 901657 (W.D. Wash. Mar. 29, 2006) (holding state-law failure-to-warn claims not preempted); *Peters* v. *Astrazeneca, LP*, 417 F. Supp. 2d 1051 (W.D. Wis. 2006) (same); *Cartwright* v. *Pfizer, Inc.*, 369 F. Supp. 2d 876 (E.D. Tex. 2005) (same); *Zikis* v. *Pfizer, Inc.*, 2005 WL 1126909 (N.D. Ill. May 9, 2005) (same); *Witczak* v. *Pfizer, Inc.*, 377 F. Supp. 2d 726 (D. Minn. 2005) (same); *Caraker* v. *Sandoz Pharm. Corp.*, 172 F. Supp. 2d 1018 (S.D. Ill. 2001) (same); *Mazur* v. *Merck & Co.*, 742 F. Supp. 239 (E.D. Pa. 1990) (same).[5] Indeed, one recent decision—holding, contrary to

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situations in which state law, although not physically incompatible with federal law, nonetheless impedes attainment of the federal statutory objective.

[5] As noted by the FDA in the Preemption Preamble, the Vermont Supreme Court is not the only lower court to have mistakenly con-

the decision below, that state-law tort claims such as those brought by plaintiff are impliedly preempted under the FDCA—expressly recognizes the "many conflicting court decisions on this topic." *Colacicco* v. *Apotex, Inc.*, 432 F. Supp. 2d 514, 518 (E.D. Pa. 2006), appeal docketed, No. 06-3107 (3d Cir. June 21, 2006). See also *McNellis* v. *Pfizer, Inc.*, 2006 WL 2819046, at *12 (D.N.J. Sept. 29, 2006) (reaffirming decision holding that state-law failure-to-warn claims are not preempted but certifying issue for interlocutory appeal given acknowledged "split in authority"), appeal docketed, No. 06-5148 (3d Cir. Dec. 27, 2006).

The question of FDCA preemption is an extremely important one. It directly affects tens of thousands of cases that are currently pending. See Pet. 13 n.4. Moreover, it implicates substantial policy issues affecting both public health and interstate commerce (in the pharmaceutical industry and beyond). See *supra* at 4–10.

Although there is, as of yet, no circuit split on the issue, this Court should not delay its resolution of the deep division below. Given, on the one hand, the clearly erroneous decision of the Vermont Supreme Court, and, on the other hand, the compelling arguments in favor of preemption, a conflict between a state court of last resort and a United States court of appeals on this important federal question seems highly likely, if not inevitable, as the many pending cases percolate upwards. Awaiting the probable circuit split before deciding the issue would have deleterious consequences: Courts will be burdened with large numbers of cases that should never have been filed, let alone allowed to go to trial; pharmaceuti-

---

strued FDA drug labeling requirements as setting only a floor, but not a ceiling, for state regulation of pharmaceuticals. See 71 Fed. Reg. at 3934–3935 (citing, *inter alia*, *Brochu* v. *Ortho Pharm. Corp.*, 642 F.2d 652 (1st Cir. 1981); *Salmon* v. *Parke-Davis & Co.*, 520 F.2d 1359 (4th Cir. 1975); *In re Tetracycline Cases*, 747 F. Supp. 543 (W.D. Mo. 1989)).

cal manufacturers will be caught in an inescapable dilemma, forced to choose between complying with federal law and complying with conflicting state law; and the public health will be endangered as juries impose unsubstantiated warnings that obscure valid warnings and possibly deter patients from accepting effective treatments.

This case presents the Court with an ideal vehicle for resolving the persistent conflict over FDCA preemption of state-law tort claims. The judgment below depends entirely on the resolution of the federal statutory question. There is no independent state ground to sustain the judgment below if this Court holds that plaintiff's tort claims are preempted under the FDCA. Furthermore, this case presents a factual record devoid of the confounding issues that often afflict similar cases. There is, for example, no evidence or allegation that Wyeth concealed information from the FDA or failed to comply with FDA regulations when obtaining FDA approval of the Phenergan label. Moreover, after a multiyear review that addressed the danger of inadvertent intra-arterial injection in particular, the FDA specifically directed Wyeth to retain the Phenergan label.

B. At minimum, this Court should call for the views of the Solicitor General.

In an effort to avoid and correct erroneous decisions such as that below, the FDA has filed numerous *amicus* briefs in courts around the country. See *supra* at 1 n.2. If asked, the federal government would likely be eager to offer this Court its expert opinion on the scope of implied preemption under the FDCA as well as whether review of the issue is warranted. Accordingly, given the deep division in the lower courts and the tremendous importance of the issue presented, it would be appropriate for this Court, at minimum, to call for the views of the Solicitor General in this case.

CONCLUSION

The petition for a writ of certiorari should be granted.

Respectfully submitted.

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APRIL 2007

APPENDIX

APPENDIX A

Corporate Members of the Product Liability Advisory Council (as of April 2, 2007)

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A.O. Smith Corporation
Altec Industries
Altria Corporate Services, Inc.
American Suzuki Motor Corporation
Amgen Inc.
Andersen Corporation Anheuser-Busch Companies
Appleton Papers, Inc.
Arai Helmet, Ltd.
Astec Industries
BASF Corporation
Bayer Corporation
Bell Sports
Beretta U.S.A Corp.
BIC Corporation
Biro Manufacturing Company, Inc.
Black & Decker (U.S.) Inc.
BMW of North America, LLC
Boeing Company
Bombardier Recreational Products
BP America Inc.
Bridgestone Americas Holding, Inc.
Briggs & Stratton Corporation
Brown-Forman Corporation
CARQUEST Corporation

Caterpillar Inc.
Chevron Corporation
Continental Tire North America, Inc.
Cooper Tire and Rubber Company
Coors Brewing Company
Crown Equipment Corporation
DaimlerChrysler Corporation
The Dow Chemical Company
E & J Gallo Winery
E.I. DuPont De Nemours and Company
Eaton Corporation
Eli Lilly and Company
Emerson Electric Co.
Engineered Controls International, Inc.
Estee Lauder Companies
Exxon Mobil Corporation
Ford Motor Company
Freightliner LLC
Genentech, Inc.
General Electric Company
General Motors Corporation
GlaxoSmithKline
The Goodyear Tire & Rubber Company
Great Dane Limited Partnership
Guidant Corporation
Harley-Davidson Motor Company The Heil Company
Honda North America, Inc.
Hyundai Motor America
ICON Health & Fitness, Inc.
Illinois Tool Works, Inc.

International Truck and Engine Corporation
Isuzu Motors America, Inc.
Jarden Corporation
Johnson & Johnson
Johnson Controls, Inc.
Joy Global Inc., Joy Mining Machinery
Kawasaki Motors Corp., U.S.A.
Kia Motors America, Inc.
Koch Industries
Kolcraft Enterprises, Inc.
Komatsu America Corp.
Kraft Foods North America, Inc.
Lincoln Electric Company
Magna International Inc.
Mazda (North America), Inc.
Medtronic, Inc.
Mercedes-Benz of North America, Inc.
Merck & Co., Inc.
Michelin North America, Inc.
Microsoft Corporation
Mine Safety Appliances Company
Mitsubishi Motors North America, Inc.
Nintendo of America, Inc.
Niro Inc.
Nissan North America, Inc.
Nokia Inc.
Novartis Consumer Health, Inc.
Novartis Pharmaceuticals Corporation
Occidental Petroleum Corporation
PACCAR Inc.

Panasonic
Pfizer Inc.
Porsche Cars North America, Inc.
PPG Industries, Inc.
Purdue Pharma L.P.
Putsch GmbH & Co. KG
The Raymond Corporation
Raytheon Aircraft Company
Remington Arms Company, Inc.
Rheem Manufacturing
RJ Reynolds Tobacco Company
Sanofi-Aventis
Schindler Elevator Corporation
SCM Group USA Inc.
Shell Oil Company
The Sherwin-Williams Company
Smith & Nephew, Inc.
St. Jude Medical, Inc.
Sturm, Ruger & Company, Inc.
Subaru of America, Inc.
Synthes (U.S.A.)
Terex Corporation
Textron, Inc.
TK Holdings Inc.
The Toro Company
Toshiba America Incorporated
Toyota Motor Sales, USA, Inc.
TRW Automotive
UST (U.S. Tobacco)
Vermeer Manufacturing Company

The Viking Corporation
Volkswagen of America, Inc.
Volvo Cars of North America, Inc.
Vulcan Materials Company
Water Bonnet Manufacturing, Inc.
Watts Water Technologies, Inc.
Whirlpool Corporation
Wyeth
Yamaha Motor Corporation, U.S.A.
Yokohama Tire Corporation
Zimmer, Inc.

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(16)

No. 06-1249

Supreme Court, U.S.
FILED
MAY 27 2008
OFFICE OF THE CLERK

IN THE

Supreme Court of the United States

WYETH,

Petitioner,

v.

DIANA LEVINE,

Respondent.

ON WRIT OF CERTIORARI TO
THE VERMONT SUPREME COURT

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SUPERIOR COURT
WASHINGTON SMALL CLAIMS COURT

Docket No. 670-12-01 Wncv

LEVINE vs. AMERICAN HOME PRODUCTS CORP.

Case Type:
Case Track: Not set
Case Status: Disposed
Court/Jury: Jury Trial
Next Hearing:

Last judge: Geoffrey W. Crawfor
Recused: Alan W. Cook

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p# 2	def	American Home Products Corp.	O'Rourke, R. Joseph	786-1000

DISPUTES

Dspt	Case	Name	Disputants	Dispo	Date
1	cmpl	Negligence	p#1 v p#2	jplfjt	03/12/04

MOTIONS/PETITIONS/REQUESTS FOR RELIEF

No.	Type	Status	Judge	Date
1	M/For Admission of Counsel (Grossi)	granted	MT	12/09/02

2	M/For Admission of Counsel (Petersen)	denied	GWC	08/02/04
3	M/For Admission of Counsel (Pariser)	denied	GWC	08/02/04
4	M/to Amend Complaint	granted	MT	04/03/03
5	M/for Summary Judgment	denied	AWC	12/23/03
6	M/in Limine (Phenergan Injection)	denied	AWC	02/20/04
7	M/in Limine (Black Box Warnings)	denied	AWC	02/20/04
8	M/in Limine (Dilution of Phenergan)	defer	AWC	02/20/04
9	M/in Limine (Corporate Intent)	granted	AWC	02/20/04
10	M/in Limine (Vistaril)	denied	AWC	02/20/04
11	M/in Limine to Exclude Unfairly Prej. Evid	defer	AWC	02/20/04
12	M/For Admission of Counsel			03/05/04
13	M/in Limine—Prior Claims			03/05/04
14	M/Emergency Request to Postpone Trial	moot	AWC	03/05/04
15	M/for Judgment as a Matter of Law			03/11/04
16	M/to Exclude Deposition Testimony	moot	GWC	03/09/04

17	M/for Judgment as a Matter of Law			03/11/04
18	M/(Assented) to Mo. for Enlargement of Tim	granted	GWC	03/31/04
19	M/for Judgment (Renewed) as a Matter of La	judge	GWC	05/20/04
20	M/for New Trial	judge	GWC	05/20/04

12/17/01 Diana Levine, Plaintiff.

(now Wyeth) American Home Products Corp. Defendant.

Negligence case filed by Plaintiff Diana Levine against Defendant (now Wyeth) American Home Products Corp. Jury trial requested.

Jury trial requested by Plaintiff Diana Levine.

Discovery: Discovery Certificate serving Plf's 1st Interrogs & Requests to produce filed by Atty Rubin.

letter advising of docket number assigned letter sent to Plaintiff Diana Levine.

* * *

01/22/02 Appearance entered by R. Joseph O'Rourke on behalf of Defendant (now Wyeth) American Home Products Corp.

Answer filed by Attorney R. Joseph O'Rourke for Defendant (now Wyeth)

American Home Products Corp.

Jury trial requested by Defendant (now Wyeth) American Home Products Corp.

Discovery: Discovery Certificate serving Deft's 1st Expert Interrogs & requests for production filed by Atty O'Rourke.

* * *

03/07/03 MPR 4) Motion to Amend Complaint filed by Plaintiff Diana Levine. Motion to Amend Complaint. Documents filed: Mo. to Amend Complaint; Memorandum; attachments.

* * *

04/03/03 Entry Order re MPR 4) Motion to Amend Complaint. M/Reaction Form. granted by MT. See Order.

Copies of Order mailed to counsel letter sent to Plaintiff Diana Levine and Defendant (now Wyeth) American Home Products Corp. and Co-counsel for Defendant Daniel S. Pariser and Co-counsel for Defendant Cara M. Petersen and Co-counsel for Defendant Peter T. Grossi, Jr.

* * *

05/15/03 MPR 5) Motion for Summary Judgment filed by Co-counsel for Defendant Peter T. Grossi, Jr. Motion for Summary Judgment. Documents filed: Mo. for Summary Judgment or; alternarively Partial Summary Judgment; Certificate of Service; Statement of Undisputed Material Facts; Memorandum of points in support; Exhibits.

* * *

07/18/03	Party 1 filed response to MPR 5.
08/05/03	Party 2 filed response to MPR 5.
	* * *
09/09/03	Party 1 filed response to MPR 5.
	* * *
11/10/03	Motion, Petition, Request held. AWC/CH.
	Entry Order by Judge Alan W. Cook: Mo. for Summary Judgment; under advisement.
	Case status changed.
	* * *
12/19/03	1 document filed by Attorney Richard I. Rubin for party 1: Amended Complaint.
12/23/03	Decision re: Wyeth's Mo. for Summary Judgment filed.
	MPR 5 status changed to denied.
	Copies of Order mailed to counsel letter sent to Plaintiff Diana Levine and Defendant (now Wyeth) American Home Products Corp. and Co-counsel for Defendant Daniel S. Pariser and Co-counsel for Defendant Cara M. Petersen and Co-counsel for Defendant Peter T. Grossi, Jr.
	Case status changed.
01/02/04	3 documents filed for party 5: Answer of Deft Wyeth to Plf's amended; complaint; Certificate of Service.
	* * *
03/08/04	Original Emergency request to Postpone trial filed by Atty O'Rourke.

Party 2 filed response to MPR 13.

Jury Trial held. GWC/CH.

03/09/04 MPR 16) Motion to Exclude Deposition Testimony filed by Plaintiff Diana Levine. Motion to Exclude Deposition Testimony. Documents filed: Mo. to Exclude Deposition Testimony; Exhibits.

MPR 16 status changed to moot.

Jury Trial held. GWC/CH.

03/10/04 Jury Trial held. GWC/CH.

03/11/04 MPR 15) Motion for Judgment as a Matter of Law filed by Defendant (now Wyeth) American Home Products Corp. Motion for Judgment as a Matter of Law. Documents filed: Wyeth's Mo. for Judgment as a Matter of; Law; Attachment.

MPR 17) Motion for Judgment as a Matter of Law filed by Defendant (now Wyeth) American Home Products Corp. Motion for Judgment as a Matter of Law. Documents filed: Wyeth's Mo. for Judgment as a Matter of; Law; Attachment.

Jury Trial held. GWC/RP.

Entry Order by Judge Geoffrey W. Crawford: Jay Young, Court Reporter.

03/12/04 3 documents filed by Attorney R. Joseph O'Rourke for party 2: Wyeth's supplemental proposed Jury; instructions; Certificate of Service. 1 document filed by Attorney Richard I. Rubin for party 1: Proposed Jury Instructions.

2 documents filed by Attorney R. Joseph O'Rourke for party 2: Wyeth's Supplemental Preliminary; Proposed Jury Instructions.

Jury Trial held. GWC/RP.

Entry Order by Judge Geoffrey W. Crawford: Jay Young, Court Reporter.

Verdict reached for the Plaintiff, $7.4 million.

Dispute 1 disposed: Judgment for Plaintiff—Jury Trial.

03/17/04 Entry Order by Judge Geoffrey W. Crawford: See Judgment Order dated 3/17/04.

Copies of Order mailed to counsel letter sent to Plaintiff Diana Levine and Defendant (now Wyeth) American Home Products Corp. and Co-counsel for Defendant Daniel S. Pariser and Co-counsel for Defendant Cara M. Petersen and Co-counsel for Defendant Peter T. Grossi, Jr.

* * *

04/16/04 MPR 19) Motion for Judgment (Renewed) as a Matter of La filed by Defendant (now Wyeth) American Home Products Corp. Motion for Judgment (Renewed) as a Matter of La. Documents filed: Renewed Mo. for Judgment as a matter of; law; Memorandum in support of Mo; attachments; Certificate of Service.

MPR 20) Motion for New Trial filed by Defendant (now Wyeth) American Home Products Corp. Motion for New Trial.

Documents filed: Mo. for New Trial on Damages; Memorandum in support of Mo; attachments; Certificate of Service.

05/20/04 Party 1 filed response to MPR 19.

Party 1 filed response to MPR 20.

1 document filed by Attorney Richard I. Rubin for party 1: Transcripts (5) binders.

MPR's 19-20: 19)Motion for Judgment (Renewed) as a Matter of La; 20) Motion for New Trial given to Judge Geoffrey W. Crawford.

06/07/04 Party 2 filed response to MPR 20.

* * *

08/02/04 Decision on Motion for Judgment Under VRCP 50 filed.

MPR 2-3 status changed to denied.

Copies of Order mailed to counsel letter sent to Plaintiff Diana Levine and Defendant (now Wyeth) American Home Products Corp. and Co-counsel for Defendant Daniel S. Pariser and Co-counsel for Defendant Cara M. Petersen and Co-counsel for Defendant Peter T. Grossi, Jr.

* * *

09/01/04 Notice of Appeal & $225.00 filing fee filed by Atty O'Rourke.

* * *

10/06/04 Order Amending Rule 50 Decision filed.

Copies of Order mailed to counsel letter sent to Plaintiff Diana Levine and Defen-

dant (now Wyeth) American Home Products Corp. and Co-counsel for Defendant Daniel S. Pariser and Co-counsel for Defendant Cara M. Petersen and Co-counsel for Defendant Peter T. Grossi, Jr.

Pltf's 9/7/04 letter and Court's 10/6/04 Order forwarded to Vt. Supreme Court.

10/30/06 Entry Order filed by Vermont Supreme Court affirming decision.

12/11/06 Copy of Entry Order filed by Vt. Supreme Court: "Appellant has filed a timely motion for reargument of this court's October 27, 06 decision in the above matter. Insofar as appellant has failed to demonstrate that the court overlooked or misapprehended points of law or fact that would have affected the result, the motion is denied. VRCP 40.

12/18/06 Entry Order filed by Supreme Court advising motion for reargument is denied.

* * *

01/25/07 Entry Order filed by VT Supreme Court: "The mandate in the opinion issued by this Court on October 27, 2006 is stayed pursuant to the parties' stipulation entered into on January 16, 2007. As agreed in the stipulation, the stay will expire upon either the United States Supreme Court's denial of appellant's petition for a writ of certiorari or, if the writ is granted, affirmance of this Court's decision.

* * *

SUPREME COURT OF VERMONT

2004-384 Heard

Printed: Mon May 12 2008 at 10:16:49
From Washington Superior Appeal Civil
Orig. Dkt. # 670-12-01 Wncv
Judge(s) ; Crawford G; Cook A; Teachout M

DIANA LEVINE, Appellee,

v.

WYETH*, Appellant.

	Date Due	Filed/ Waived	Prog Order Issued
Filed in Trial Court OR Board:		09/01/2004	
Notice of Appeal:		09/07/2004	
Trans. Ordered:	09/15/2004	11/11/1111	
AA Docking Stmt:	09/15/2004	09/17/2004	
AE Docking Stmt:	10/01/2004	09/20/2004	
Record Complete:	11/10/2004	09/17/2004	
Appellant Brief:	11/19/2004	11/22/2004	Yes
Appellee Brief:	01/18/2005	01/21/2005	Yes
Considered on:	10/05/2005	Argued	
Decided:	10/27/2006	cwoj	aff

Counsel for 2004-384
Appellee's Attorney(s)
1096 Rubin, Richard, I.
Appellant's Attorney(s)
975 O'Rourke, R., J.
100 Pro Se

DOCKET ENTRIES for 2004-384

* * *

09/07/2004 Notice of Appeal received. Original notice filed in trial court 09/01/2004. Entry fee paid by American Home Products. Case file (in large box) and docket entries rec'd from tc. TC will retain exhibits until requested.[1]

* * *

01/20/2005 Complied AAB filed by Atty. Keyes.

01/21/2005 AEB & SPC fi by Atty. Rubin.

02/08/2005 ARB fi by Atty. Keyes.

* * *

10/05/2005 Transcripts rec'd from Atty. Keyes—3/8/04 (3 volumes), 3/9/04 (2 volumes), 3/10/04, 3/11/04 and 3/12/04.

HEARD BY FULL COURT. PLR, JAD, DRJ, FWA and Walter Morris. Attys Keyes and Rein and Rubin argued.

* * *

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[1] Clerk's notations indicating name of person who added docket entry deleted.

10/27/2006 ENTRY ORDER; PLR, JAD, DRJ, FWA and Morris, D.J.; Johnson author, Reiber dissenting: Affirmed. cc of EO and opinion to counsel, trial court, trial judge.

* * *

11/13/2006 Motion for Reargument fi by Atty. Keyes. CC'd Attys. Rubin, Pariser, Wiley, Rein & Felding.

* * *

12/11/2006 ENTRY ORDER. PLR, JAD, DRJ, Walter K. Morris, Jr. and Frederic W. Allen. Appellant has filed a timely motion for reargument of this Court's 10/27/06 decision in the above matter. Insofar as appellant has failed to demonstrate that the Court overlooked or misapprehended points of law or fact that would have affected the result, the motion is denied. cc of EO to counsel and tc.

12/14/2006 Wyeth's Motion to Stay Issuance of Mandate Pending Application to the US Supreme Court for Disposition of Writ of Certiorari fi by Atty. Keyes, cc'd Attys. Rubin and Pariser.

12/19/2006 Ms. Levine's Response to Wyeth's Motion to Stay Mande fi by Atty. Rubin, cc'd Atty. Keyes.

12/22/2006 Wyeth's Reply in Support of its Motion to Stay Mandate fi by Atty Keyes, cc'd Attys. Rubin and Pariser.

* * *

01/19/2007 Stipulation Regarding Conditions of Stay filed & signed by Attys. Keyes & Rubin. Gate to EAM.

01/23/2007 ENTRY ORDER. DRJ. The mandate in the opinion issued by this Ct. on 10/27/06 is stayed pursuant to the parties' stip. entered into on 1/16/07. As agreed in the stip., the stay will expire upon either the US Supreme Court's denial of appellant's petition for a writ of certiorari or, if the writ is granted, affirmance of this Court's decision. cc of EO to counsel and tc.

* * *

01/22/2008 Ltr. rec'd from the US Supreme Court. The Petition for a Wit of Certiorari is granted. Petitioner's brief is due 2/25/08, respondent's brief is due 3/24/08 and ARB is due according to the rules of the US Supreme Court.

* * *

STATE OF VERMONT
WASHINGTON COUNTY, SS.

DIANA LEVINE	)	
	)	WASHINGTON SUPERIOR
v.	)	COURT
	)	DOCKET NO. 670-12-01 Wnev
WYETH	)	

AMENDED COMPLAINT

Diana Levine says:

1. Diana Levine lives in Marshfield, Vermont and on April 7, 2000 was patient at the Health Center in Plainfield, Vermont.

2. On April 7, 2000, she went to the Health Center complaining of migraine headache and received an intravenous injection of Phenergan®, which was manufactured by the defendant, American Home Products (AHP).

3. AHP is a pharmaceutical company and sells its products, including Phenergan®, in Vermont.

4. Diana Levine was given the contents of two 25 mg tubex' of Phenergan®, which were transferred intravenously into the antecubital space of her right arm without further dilution.

5. The Phenergan® given to Diana Levine was defective. The product information failed to instruct the clinician administering the drug to dilute the drug; it also failed to instruct the clinician to administer the drug through a running IV. The product information also failed to provide sufficient and adequate warnings that intra-arterial injection or extravasation could cause irreversible gangrene and loss of limb. The

Phenergan® was not reasonably safe due to inadequate warnings and instructions regarding foreseeable risks of harm.. If adequate instructions concerning the proper administration and dilution of Phenergan® had been provided to health care providers known to administer the drug intravenously, the physician's assistant administering the IV would have taken appropriate measures to reduce the risks of harm in accordance with the warnings and instructions.

6. The Phenergan® sold by the defendant is also not reasonably safe for intravenous administration because the foreseeable risks of harm posed by the intravenous administration of the drug are sufficiently great in relation to its foreseeable therapeutic benefits that reasonable health care providers, knowing of such foreseeable risks and benefits, would not prescribe the drug intravenously for any class of patients.

7. The clinician at the Health Center inadvertently administered the drug into an artery, or into the tissue outside the intended vein (extravasation). Such an occurrence is a forseeable consequence of IV drug administration.

8. As result of the defective drug, Diana Levine suffered extreme pain, suffering, two amputations of her right arm (the second midway between the wrist and elbow), loss of livelihood, and extreme emotional anguish.

9. Diana Levine is musician. She can no longer play the bass guitar and piano. She had a successful music production business which is no longer viable.

10. The defendant has known since 1987 that its instructions were inadequate and unsafe insofar as they stated that Phenergan could safely be administered intravenously without using a running IV. A running IV

is an intravenous administration method which utilizes a bag of saline suspended above the patient and connected by means of an indwelling catheter to the patient's vein. The saline in the bag will flow by gravity through plastic tubing into the vein. Medication can be administered through a side port in the tubing into the flowing saline, or added to the bag of saline itself.

11. In 1988, the defendant prepared new instructions for its product insert which made clear that Phenergan must be administered intravenously only through a running IV in order to ensure adequate dilution and guarantee venous placement.

12. The defendant has known for more than 25 years of the grave risks associated with inadvertent arterial injection or extravasation of Phenergan, including irreversible gangrene and amputation.

13. The defendant knew, from at least 1988, that instructions requiring administration of Phenergan intravenously only through running IV could prevent inadvertent arterial injection and extravasation along with its catastrophic results.

14. From 1988 through 2000, the defendant was aware that inadvertent arterial injection and extravasation continued to cause severe injury to patients receiving Phenergan intravenously.

15. Wyeth stated on multiple occasions:

> When implemented this [revised] warning will incorporate the "best thinking" of both Wyeth-Ayerst and the division in regard to prevention of misinjection should it occur. Since misinjection may cause severe tissue injury (including necrosis with resultant gangrene and amputation) we believe that the use of the updated

warning is of critical importance for the safe use of Phenergan injection.

16. Despite its knowledge of the continued occurrence of injury and the fact that revised instructions would lessen or completely avoid the harms associated with intravenous administration, the defendant chose not to revise its product insert and instructions.

17. The defendant had a duty to revise its product insert to prevent the foreseeable harm that would occur upon misinjection.

18. If the defendant had revised its instructions to require that Phenergan only be administered through a running IV, the injury to Diana Levine would not have happened. The failure to revise the instructions was the proximate cause of her injury.

19. The conduct of the defendant was negligent, grossly negligent, wanton, willful, and totally unjustified.

20. The negligence and/or gross negligence was the proximate cause of the plaintiff's injuries.

WHEREFORE, Diana Levine seeks appropriate damages for her loss.

Dated at Barre, Vermont this 18 day of December 2003.

Respectfully submitted,

DIANA LEVINE

By: /s/ _____

Richard I. Rubin, Esq.

STATE OF VERMONT
WASHINGTON COUNTY, SS.

Diana Levine Plaintiff,	))
v.	) Washington Superior Court) Docket No. 670-12-01 Wncv
American Home Products, Inc. (now Wyeth), Defendant.	)))

Stamp: FILED
(initials)
2003 DEC 23 P 1:08
SUPERIOR COURT
WASHINGTON COUNTY

Decision re: Wyeth's Motion for Summary Judgment

Plaintiff Diana Levine alleges that she suffered harm from the improper administration of a drug which itself was caused by insufficient warnings on the drug's label. Defendant Wyeth, manufacturer of the drug, has filed a motion for summary judgment. Defendant is represented by Peter T. Grossi, Jr., Esq. Plaintiff is represented by Richard I. Rubin, Esq. For the following reasons, Wyeth's motion for summary judgment is denied.

The basic facts of this case are undisputed. Plaintiff has a long history of suffering debilitating migraine headaches. As she had done many times previously, on April 7, 2000, Plaintiff visited Northeast Washington County Community Health, Inc. (the Health Center)

for treatment of an episode. A nurse acting on the instruction of a physician assistant gave Plaintiff an intramuscular injection of Demerol (for pain) and Phenergan Injection (for nausea). Though this combination had provided relief in the past, on April 7 it was ineffective. Plaintiff returned to the Health Center later in the day.

Jessica Fisch, a physician assistant, treated Plaintiff on her return. Fisch decided to administer a second dose of Demerol and Phenergan Injection. However, rather than injecting it intramuscularly as Plaintiff typically received it, Fisch attempted to inject the medication intravenously using a "butterfly infusion set." Fisch inadvertently injected the medication into an artery rather than the intended vein. The parties do not dispute that this inadvertent intra-arterial injection of Phenergan caused the necrosis and gangrene that led to the amputation of Plaintiff's arm just below the elbow. The parties also do not dispute that the FDA approved label for Phenergan plainly discloses the high risk of necrosis and gangrene leading to amputation if Phenergan is inadvertently injected intra-arterially. Other facts are mentioned below as necessary

Plaintiff claims that the warnings in the label about intra-arterial injection of Phenergan are inadequate and that inadequacy proximately caused Plaintiff's injuries. The allegations of inadequacy focus primarily on whether intravenous injection is appropriate in any circumstances at all, and if so, how precisely it must be done to obviate the extreme risk of harm attending intravenous injection. Denying any inadequacies in these regards, Wyeth asserts three grounds for summary judgment: 1) the "failure to warn: claim is pre-empted by the supremacy of federal law; 2) there is no proximate causation; and, in any event, 3) Plaintiff's claim for

punitive damages lacks of any evidentiary support. On the current record, the court cannot conclude that Wyeth is entitled to judgment as a matter of law with regard to any of these issues.

Preemption

Plaintiff asserts two preemption arguments: field preemption and conflict preemption. Field preemption refers to instances where state law "regulates conduct in a field that Congress intended the Federal Government to occupy exclusively," whereas conflict preemption refers to situations where "it is impossible for a private party to comply with both state and federal requirements." Motus v. Pfizer Inc., 127 F.Supp.2d 1085, 1091 (C.D.Cal 2000) (quoting English v. General Elec. Co., 496 U.S. 72, 78-79 (1990)). The two theories often overlap. Wyeth makes both overlapping arguments, which the court addresses separately.

With regard to field preemption, Wyeth argues that the FDA's regulatory activity is so extensive with regard to the content of drug labels that state tort law actions asserting failure to warn claims effectively are preempted as a matter of law. Wyeth concedes that nearly all cases addressing this issue have concluded that the FDA;s drug labeling activity sets a floor, not a ceiling, on the strength of the language in the labeling, and hence preemption usually does not occur. See Wyeth's Memorandum of Points and Authorities at 14 n.4 (filed May 15, 2002). Nevertheless, Wyeth argues that cases so holding are outdated in light of recent United States Supreme Court cases such as Buckman Co. v. Plaintiffs' Legal Committee, 531 U.S. 341 (2001). After carefully reviewing the authorities, the court is persuaded that neither Buckman nor other United States Supreme Court cases compel the conclusion

urged by Wyeth and that the exhaustive analyses in lower federal court cases rejecting preemption—such as Caraker v. Sandoz Pharmaceuticals Co., 172 F.Supp.2d 1018, 1030-1044 (S.D. Ill. 2001) and Motus, 127 F.Supp.2d at 1091-1100—are valid and sound. The court adopts the reasoning of Caraker and Motus and rejects Wyeth;s field preemption argument.

Wyeth also argues that the facts specifically relating to this case demonstrate an actual conflict between a specific FDA order with which it was obligated to comply and Plaintiff's failure to warn action. There is evidence suggesting that Wyeth at least at one time may have considered strengthening the label warning with regard to intra-arterial injection. In that regard, Wyeth has submitted a document dated August 22, 1988 denominated "Amplification of Draft Labeling Submitted May 3, 1988." Appendix to Wyeth's Memorandum of Points and Authorities. The document includes notes on a Phenergan label with ostensibly proposed revisions including stronger language about intra-arterial injection. Wyeth then cites to a February 21, 1997 letter from the FDA to Wyeth regarding your "supplemental new drug application dated September 21, 1981 ... for Phenergan (promethazine hydrochloride) Injection. Appendix G to Wyeth's Memorandum of Points and Authorities. The following sections are relevant:

> We have completed the review of this supplemental application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to submit final printed labeling (FPL) revised as follows.
>
> > The following comments are provided regarding the version of the Phenergan Tubex and

> Ampul labeling submitted in the August 6, 1996 amendment. Please note that the term "current labeling" refers to these versions.

The tenth numbered section of comments states, in relevant part:

> 10. The WARNINGS section should be modified to read as follows.
>
> SULFITE SENSITIVITY—
>
> ...
>
> f. **Inadvertent Intra-arterial Injection**—Retain verbiage in current label.

Without any evidentiary basis other than the two documents mentioned above, Wyeth argues that the phrase "Retain verbiage in current label" foreclosed any possibility of incorporating into the label the sort of stronger warning that Plaintiff urges was necessary, and that appears more or less in the notes on the August 22, 1988 document.

On this record, Wyeth's analysis is highly speculative at best. The February 21, 1997 letter specifically states that the term "current labeling" refers to the "labeling submitted in the August 6, 1996 amendment." Wyeth however asserts that the expression "current label" in paragraph 10(f) refers to the labeling then in effect, rather than the labeling in the August 6, 1996 amendment. Wyeth later clarifies that the labeling in the August 6, 1996 amendment is the same as the labeling then in effect. Whatever the truth may be, the record includes no evidence of any kind implying that the expression "Retain verbiage in current label" has the dual meaning Wyeth advances: that the "current" language must be retained while the language proposed in the August 22, 1988 document is forbidden. As a more

general matter, no record evidence suggests that Wyeth earnestly attempted to alter the label to strengthen the warning about intra-arterial injection, and that the FDA specifically disallowed the strengthened language. The record as currently developed lacks any evidence that the FDA set a ceiling on this matter. Accordingly, the court discerns no basis for conflict preemption.

Proximate Causation

Assuming arguendo that the warnings in the label were inadequate as alleged, Wyeth argues that Plaintiff will not be able to prove that the inadequacy proximately caused the harm. Wyeth's argument is straightforward: even if the label included different instructions, Fisch would not have followed them. Plaintiff asserts the contrary and argues that the issue should be reserved for the jury.

The Vermont Supreme Court adopted strict products liability as embodied in Restatement (Second) of Torts § 402A in Zaleskie v. Joyce, 133 Vt. 150, 154-55 (1975). Consistent with § 402A, the Vermont Supreme Court adopted the so called "read and heed" rule in failure to warn cases. :Where warning is given, the seller may reasonably assume that it will be read and heeded; and product bearing such a warning, which is safe for use if it is followed, is not in defective condition, nor is it unreasonably dangerous." Restatement (Second) of Torts § 402A cmt. j. "In effect, a presumption of causation is created in failure-to-warn cases. This does not impose absolute liability on the manufacturer, but merely shifts the burden to the manufacturer to go forward with the evidence." Menard v. Newhall, 135 Vt. 53, 54-55 (1977). Both parties causation arguments presume the applicability of the read and heed rule to

this case.[2] Wyeth seeks to overcome the presumption of causation with evidence that Fisch disregarded the label's warning and thus would have disregarded any strengthened warning.

While Wyeth's argument is not without meaningful evidentiary support, competing evidence also supports a contrary conclusion. The court need not dwell on the atomies of that dispute here, however; it is sufficient to document its existence in light of Wyeth's burden. Additionally, as is common in this type of case, the issue of the adequacy of the warning and the issue of causation overlap. See Town of Bridport v. Sterling Clark Lurton Corp., 166 Vt. 304, 310 (1997) (adequacy and causation "closely intertwined"). Plaintiff has come forward with evidence sufficient to foreclose judgment as a matter of law on the issue of adequacy of the warning. Both issues therefore must be resolved finally by the jury. See id, at 311 ("ordinarily the sufficiency of [the] warning is a question for the jury).

Punitive Damages

Lastly, Wyeth argues that Plaintiff's claim for punitive damages should be dismissed for lack of any evidentiary support whatsoever. Plaintiff responds to this argument by asserting without any evidentiary support that the court should assume for purposes of the summary judgment decision that Wyeth maliciously refused to alter the Phenergan label for the sole purpose of maximizing profits in patent dereliction of patient

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[2] At least some courts have held that in certain circumstance the read and heed rule does not create a presumption of causation in failure to warn cases against pharmaceutical manufacturers. See, e.g., Motus v. Phizer Inc., 196 F.Supp.2d 984, 992-94 (2001).

safety. The court declines to draw such an inference without evidentiary support. Nevertheless, the development of evidence which could support punitive damages appears at least to be possible. "Before the court can apply the law, it must have an adequate factual basis for doing so." 10A C. Wright & A. Miller, Federal Practice and Procedure § 2725, at 412. Judgment on this issue is premature at this time.

Order

For the foregoing reasons, Wyeth's motion for summary judgment is DENIED.

Dated at Montpelier, Vermont this 23rd day of December, 2003.

/s/_____
Alan W. Cook
Superior Court Judge

STATE OF VERMONT
WASHINGTON COUNTY, SS.

DIANA LEVINE Plaintiff v. AMERICAN HOME PRODUCTS, INC. (now) WYETH Defendant	Washington Superior Court Docket No. 670-12-01 Wncv

ANSWER OF DEFENDANT WYETH TO PLAINTIFF'S AMENDED COMPLAINT

COMES the Defendant, Wyeth, by its attorneys and respectfully answers the Plaintiff's Amended Complaint and says as follows:

1. Wyeth has no particular information as to the allegations in Paragraph 1 and therefore denies the same and leaves the Plaintiff to her proof.

2. Wyeth has no particular information as to the allegations in Paragraph 2 and therefore denies the same and leaves the Plaintiff to her proof.

3. Wyeth admits Paragraph 3.

4. Wyeth has no particular information as to the allegations in Paragraph 4 and therefore denies the same and leaves the Plaintiff to her proof.

5. Wyeth has no particular information as to the allegations in Paragraph 5 and therefore denies the same and leaves the Plaintiff to her proof.

6. Wyeth denies Paragraph 6.

7. Wyeth has no particular information as to the allegations in Paragraph 7 and therefore denies the same and leaves the Plaintiff to her proof.

8. Wyeth has no particular information as to the allegations in Paragraph 8 and therefore denies the same and leaves the Plaintiff to her proof.

9. Wyeth has no particular information as to the allegations in Paragraph 9 and therefore denies the same and leaves the Plaintiff to her proof.

10. Wyeth denies the allegations in the first sentence of Paragraph 10. Wyeth states that there are a variety of methods of intravenous administration including by use of a bag of saline suspended above the patient and connected by means of an indwelling catheter to the patient's vein, which will flow by gravity or by mechanical means. Wyeth otherwise denies the remaining allegations in Paragraph 10.

11. Wyeth denies the allegations in Paragraph 11.

12. Wyeth states that it has known of the risks associated with inadvertent intra-arterial injection of Phenergan® Injection for many years and that it has adequately warned of those risks during all relevant time periods. Wyeth otherwise denies the allegations in Paragraph 12.

13. Wyeth denies the allegations in Paragraph 13.

14. Wyeth denies the allegations in Paragraph 14.

15. Wyeth admits that the language quoted in Paragraph 15 of Plaintiff's Amended Complaint appeared in Annual Reports for Phenergan® Injection submitted to FDA for the years 1989 through 1995. Wyeth further states that the allegations in Paragraph 15 seek to characterize writing, to which no response is required, but, if response is deemed necessary, Wyeth states that the referenced writing speaks for itself and any attempt to characterize the writing is expressly denied.

16. Wyeth admits that it did not adopt the draft labeling changes submitted to FDA on May 3, 1988, referenced at Exhibit 4 to Plaintiff's Motion to Amend Complaint (NDA 00005337-00005348). Wyeth otherwise denies the allegations in Paragraph 16.

17. Wyeth states that Paragraph 17 states a legal conclusion to which no response is required, but, if a response is deemed necessary, Wyeth denies the allegations in Paragraph 17

18. Wyeth states that Paragraph 18 states a legal conclusion to which no response is required, but, if a response is deemed necessary, Wyeth denies the allegations in Paragraph 18.

19. Wyeth states that Paragraph 19 states a legal conclusion to which no response is required, but, if a response is deemed necessary, Wyeth denies the allegations in Paragraph 19.

20. Wyeth states that Paragraph 20 states a legal conclusion to which no response is required, but, if a response is deemed necessary, Wyeth denies the allegations in Paragraph 20.

FIRST SEPARATE AND COMPLETE DEFENSE

The Complaint fails to state claim upon which relief can be granted at the Washington Superior Court.

SECOND SEPARATE AND COMPLETE DEFENSE

The Defendant says that the Plaintiff herself was negligent and/or any intervening parties were negligent, which negligence is expected to be determined through discovery. The Plaintiff and/or the Interveners' negligence was greater in kind and degree than any negligence on the part of the Defendant, which negligence on its part, it denies, and because of the Plaintiff's negligence and/or the Interveners' negligence, Plaintiff cannot recover against the Defendant.

THIRD SEPARATE AND COMPLETE DEFENSE

Plaintiff's alleged injuries and damages were not proximately caused by any act or omission by Defendant.

FOURTH SEPARATE AND COMPLETE DEFENSE

The damages alleged by Plaintiff were caused or proximately caused by some person(s) or third party other than Defendant and for whom Defendant is not legally responsible.

FIFTH SEPARATE AND COMPLETE DEFENSE

Plaintiff's claims, including but not limited to Plaintiff's claim for punitive damages, are barred in whole or in part by the doctrine of federal preemption.

DEMAND FOR JURY TRIAL

The Defendant demands Jury Trial on all issues.

Dated at Washington, D.C. this 31st day of December, 2003.

WYETH

By: /s/_____

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EXCERPTS OF TRIAL TRANSCRIPT, NO. 670-12-01 (VT. SUPER. CT.)

MARCH 8, 2004

* * *

[Conference on Motions in Limine]

[8] agree that arterial injection is a no-no.

MR. RUBIN: Well, the issue in the case is instructions, not that this can happen.

THE COURT: Right.

MR. RUBIN: And over the course of 30 years there have been multiple amputations, gangrene, untoward events that have gone on continually since at least 1969 with this product. And these reports are in the FDA database available to the company, of course, many of which we got from the company itself when we requested the Adverse Reports that they had in their files. There's also literature in their files, articles, internal memos that talk about amputations and other untoward events.

Our claim is that this drug should not be introduced intravenously at all. And it's really important that as a basis of our experts' opinion that they looked at these Adverse Reports and, although the company says in its warnings watch out if it gets in an artery, you can have gangrene, the extent and degree to which this is known, the frequency that it happens, the severity of the result are all important for their determination that this drug is not safe to be used

* * *

[Opening Statement of Richard I. Rubin, Counsel for Plaintiff]

[39] arm. It's a case about Wyeth the drug company that manufactured this drug Phenergan. You'll hear a lot about Phenergan. It's a case about Wyeth, who knew that this drug was one hundred percent safe if injected in the butt intramuscularly, but they also know it posed a great risk of amputation and loss of limb if it was introduced intravenously. And it's a case about Wyeth. They had the obligation to publish instructions that would prevent this from happening. And there was a simple instruction that they could have written "Do not use this drug intravenously."

That's what the case is about. We'll have a number of experts, doctors, to tell you why is this so? Let me tell you a little bit about Diana. As I said, she lives in Marshfield. She's lived in the same house for 27 years. This accident, this tragedy, happened in April of 2000. Diana is a mother. Her daughter Jessie is here. She's a musician, highly accomplished musician. I'll talk about that more in a minute. Community member, a family member, her brother is here seated there in the tie. She was raised in upstate New York. She went to Glens Falls High School. Then she went to UVM.

* * *

[45] want to give it, but she gave it intravenously in a method that she had used 50 to 75 times before.

Now, we're going to talk about medicine and stuff and a little bit about needles. So one of the jurors—if you have any squeamishness about needles, let us know. But the science isn't complicated. It's really pretty straightforward and common sense. She gave the intravenous injection by using what's called a single

dose infusion. It's like the needle that they use to draw blood, a small needle that goes in the vein in the crook of your arm. It has a rubber hose, a tube on the back of it, and you attach that to a syringe, about three cc's of liquid, slowly load that up with your Phenergan and you slowly over two minutes push that out of the syringe a little tube through the needle which is in the vein hopefully into your arm. That's called a direct intravenous injection. IV push injection. Very common.

At the time it was given at the Health Center this way, it was a standard use of an intravenous injection and that's how it was given at Central Vermont Hospital. There is another way to give an intravenous injection that may be more common to you and that's what you see—or you've [46] had in the hospital when you have a bag, you know, on a hook and you put the tube running down the bag. And what they do is they set up the IV by putting in a soft, flexible tube or catheter and they put that in your vein and then they attach that to the tube. You've all seen that. And then they let the clear liquid saline. It's saline. They let that run and this runs down the tube through the catheter into your vein. And they let it run because it's harmless. And they let it run a couple of minutes. If it's running, they know they're in the vein because the pressure—if they're in the artery where you do not want to be, if it runs into the artery, it will back up because the pressure in the artery, you know, if you cut an artery, it spurts, so the pressure in the artery will stop—literally stop the flow of this saline from running. So if you're in the artery, it won't run. If you pierce the back of the vein so that it's under—in the tissue, which you don't want to happen because then it can bathe the artery and cause this disaster, it will form a puddle in your skin and stop running.

So if you use this flow- free-flowing IV, that's how I'll refer to it, you can be pretty [47] sure—much more sure that you will not be putting this corrosive, dangerous drug into a vein.

So first she sets up, she gets the equipment, she gets the needle for this direct infusion, she gets the—and she slowly over two minutes administers the Phenergan into the artery. She unhooks the syringe, takes a little saline, pushes that through to clear the line. She took another syringe and puts in the Demerol. Standard practice. And the practice was consistent with the instructions that were provided by Wyeth.

Now, when a drug company sells a product that's going to be administered at a hospital they have to tell the people who are administering the product how to do it. And if they can avoid risks that they know of, they have to write instructions that will avoid those risks, even if one of the risks is that the clinician might make a mistake. If they know that that can happen, and they can simply fix the problem with no significant impact on the effectiveness of the drug, they'd better do it.

She administered this drug the way she had done it before and consistent with the instructions and what happened? The drug got out [48] of the vein, bathed the artery or went directly into the artery, was corrosive, caused this spasm in the artery, the spasm spread down her forearm into her fingers. There were spasms in the little vessels, the little arteries, clots, her tissue died, she got gangrene and ultimately she lost her arm.

When she came back—she went home again, the Demerol knocked her out, she went back at four o'clock in the afternoon. Her headache was gone, but her arm was killing her and she said help me. John Matthew, who will testify, was the doctor at the Health Center.

He's actually seated in the back. He said we've got to deal with this. This is serious. So he had one of his people call Wyeth because they have a phone number where you call if there is a problem. And he called them and they said—talked to some woman there, some, you know, there's this problem with the arm swelling, and it's changing colors and it's cold. What do we do? And they said I don't know. We'll send you a form to report it. So they called the vascular surgeon up in Burlington and he said there's probably nothing you can do. You can try blood thinners, you can try this, you can try that.

* * *

[53] irreversible gangrene and loss of limb if it gets into an artery. They may say it in their warnings, and you'll hear, oh yes, we say it, but they have known for 30 years that if it leaks out of a vein it will cause tissue death, gangrene.

They've also known for 30 years that this rigid needle that was used, that butterfly system that was used by Jessica Fisch, causes extra problems. And we have memoranda from their files where they—where they talk about use of these rigid needles, these needles as opposed to the floppy catheter from the free-flowing IV, causes this—it's more likely to happen because you don't have a safety monitor and it can leak out of the vein.

They've also known for 30 years—and this is not in their warnings—that some significant percentage of us have what we call abberant arteries. Arteries in the wrong place. We're all not the same inside. There's two—three to 12 percent of us that have arteries artifically shouldn't be there. Shouldn't be there. They are where they are, but they're not normal. Three to 12

percent of us have these little vessels. Some are very close to the

* * *

[55] MR. O'ROURKE: Your Honor, this is getting into argument rather than opening statement.

THE COURT: I think that's probably a fair comment. Why don't we stick just to the facts.

MR. RUBIN: The evidence will show that Jessica Fisch, even if she was responsible, even if she made a mistake, they will say that she didn't stop when Diana may have complained of some pain when the injection was going in. The evidence will show that it probably was too late at that point.

They will also—it's also the case that since they have known for 30 years that clinicians make mistakes, that they could have fixed this problem by changing the instruction to preclude intravenous use. You'll also hear that this drug was approved by the federal Food and Drug Administration. But the evidence will be that what happens is the Food and Drug Administration relies on the drug companies to make its decision. They get their information from the drug companies, review this information, and then sign off on the labels. The approval by the Food and Drug Administration is the minimum federal standard for [56] the sale of the drug.

The court will tell you that it is your decision that you are the judges of whether the instructions in this case are safe and the product was defective or whether the company was negligent.

I want to conclude by talking a little bit about damages. We will ask for a very large amount of money here. And there's two parts to the damages. There's

kind of the economic, the numbers that we can put up on a board, and we will put up. And we will show you that the loss of her business and her ability to earn an income—we'll have experts to testify to this—over the course of the rest of her working life is approximately $600,000. And we will offer evidence that there's $225,000 roughly in medical bills and other expenses so far. And we have a Life Care Plan, which has been developed, will show what she will need for the rest of her life to at least to try and make a physical accommodation for what happened to provide therapy is about another million dollars. And these numbers are not seriously in dispute. And they total roughly $2 million. But that's the easy part.

You will also be asked to compensate

* * *

[Testimony of Dr. John Matthew]

[79] roughly?

A Yes. She was seen on that day by both Dr. Sandy Craig, who is another physician in our office, and by myself, but from that point forward—there were occasions when she saw someone else in the office, but I was supervising her care doing probably 90 or better percent of the dealing with physician's assistants and with her in the interval until she ended up being transferred to Dartmouth.

Q I'm going to ask you in a few minutes to kind of show the jury some of the equipment that is routinely used with this injection, but why don't you just take us through your understanding from the medical records of what was done.

A I think—

Q Starting in the morning when she got the first—

A When she came in the morning she saw a physician's assistant, Kim Pierce, as I recall. She had an injection, intramuscular injection of a hundred milligrams of Demerol and 50 milligrams of Phenergan.

Q Could you explain what the Demerol—I mean you heard my opening, but we have to hear from you. I'm not sure it's disputed. What does the [80] Demerol do?

A Demerol is for pain and we're trying to stop her headache. Phenergan is for — often migraines have associated vomiting or retching or nausea. The Phenergan is for sedation and nausea. Sleep can break a migraine so sedative value. It has an anti-nausea value. And Demerol itself can cause or aggravate nausea and vomiting so it prevents that side effect of the Demerol that you're using for pain.

Q Is that why you give them together?

A Yes.

Q Was the decision to give the Phenergan and the Demerol intramuscularly in the butt appropriate in the morning?

A I think it was entirely appropriate.

Q Then what happened? Did it cure the migraine?

A I gather that she went to a friend's house and slept, but she came back with the headache quite bad as I understand it, retching and she looked wretched. I saw her walk in and go down the hall and then get placed into a room that day and she looked quite terrible. She was holding her head.

[81] Q You actually remember that?

A Oh, she looked terrible.

Q Go ahead.

A So what transpired subsequently, she is in an exam room. A lot of people have migraine photophobia where light hurts. They turned down the lights, put an exam spotlight on the situation. When they got to the IV point, she was given an injection, Imitrex, which is a drug that can break a migraine. It failed to do that. I then understand that Jessica got the Phenergan, the contents of two—there is—there is a kind of injection device called a Tubex, which is like a preloaded cylinder that can go into a mechanism and become a shot. That's the only way we had Phenergan available at that time. The contents of two 25 milligram Tubexes, each having one cc, and 25 milligrams were unloaded from the Tubex and put into a three cc syringe.

Q We'll demonstrate this in a minute. Go ahead.

A She then had—Jessica then placed this butterfly IV infusion set needle in Diana's vein, having tied her arm to make the veins pop up. We chose to use butterflies in the situation—[82] butterfly needle because it can be kept quite superficial and it's short.

Q Why don't you stop. I think it might be best if I actually use some of these devices as you're going through this.

A Okay.

(Bench Conference)

MR. RUBIN: I was here in December. There was one woman in the front who has a very strong negative reaction to needles. You can see it on her face. You might ask to switch positions so she can sit in the back

row. She actually called Judge Cook last trial. She got through it, but I think it would be a good idea.

MR. O'ROURKE: I have no problem with that, your Honor. Whatever you want to do is fine with me.

(Open Court)

THE COURT: What we're going to do is we'll take our break now, but before I do that is there anybody who's nervous about needles and would like to switch position from the front to the back? They certainly can do it, just let the court officer know that you've done that when we come back so we can make sure that we know where [83] everybody is, okay? Let's take 15 minutes off now and we'll get back together just a few minutes before quarter of.

(Court recessed from 10:28 a.m. to 10:55 a.m.)

Q Before we go through actually the mechanics here, just ask a few more overview questions, Dr. Matthew. Was the decision to give the Phenergan in the afternoon by intravenous injection appropriate?

A I think it entirely appropriate.

Q Why?

A She had failed with IM earlier. Jessica wanted to get a good, higher, immediate concentration of Demerol in terms of relief of the migraine and the Demerol could induce more retching or vomiting and the 50 IM dose of Phenergan earlier had failed to control her nausea. It was a few hours later and she was still retching, so she wanted to get both a quicker, higher concentration of Demerol and an accompanying dose of Phenergan to keep her retching from getting worse and to help it.

Q Why didn't she give—why wouldn't it have been appropriate to give the Demerol intravenously, then give the Phenergan in the butt?

[84] A Because the Demerol would be circulating quickly through her brain and potentially causing her to have vomiting while the Phenergan absorbing IM would be slower and delayed so we might have aggravated her nausea and vomiting.

Q Now, you've reviewed the product insert in this case?

A I have.

MR. RUBIN: By agreement Plaintiff's Exhibit 1 is the product insert. I showed this to counsel before.

MR. O'ROURKE: No objection.

MR. RUBIN: I would offer that.

THE COURT: Okay, one is admitted.

Q I don't want you to try and read it. I want to introduce it, but I want to talk about the dosage. Was the decision to give 50 milligrams of Phenergan an appropriate dosage given the situation?

A I think so. I know that the package insert says that the usual dose is 25 I believe, but it may be used at 50 to 75 milligrams and actually is very commonly used at doses in that range. I should tell you that there are—drugs come out and they have indications that are written [85] in their package insert and they have a set of rules. Oftentimes it's not altered for quite some number of years and over time common practice will often find uses for drugs which are not listed in the initial release of the drug and the dose used or the dose range used may evolve over time. So I don't think it would be in any way unusual to find 50 milligrams to be

used in an emergency room, for example, in similar circumstances.

Q And the method of administration—you started to tell us before the break—was by use of a butterfly infusion set?

A That's correct.

Q What's that? Why don't you come down and actually show us what this is. Exhibit 22, which I've showed to counsel is the—it's a number of different pieces that went together with the—go together with the butterfly infusion sets and I would offer those now.

MR. O'ROURKE: No objection.

THE COURT: That's two.

MR. RUBIN: Twenty-two.

THE COURT: All right.

Q Why don't you—are you okay?

A This is our substitute for an arm. May [86] I take with your asking me a question—

Q Well, I have to ask you one question. What I'd like you to do is to demonstrate based on what the standard procedure and as your understanding what happened in the examining room. Starting first with the—better offer—I can offer all of these at this time. Maybe that will save time.

MR. RUBIN: Exhibit 26, Mr. O'Rourke, is a 3 cc syringe.

MR. O'ROURKE: No objection.

MR. RUBIN: Exhibit 25 is a stand around free-flowing IV setup. Offer that.

MR. O'ROURKE: No objection.

MR. RUBIN: Exhibit 23 is a Tubex, which is not a Phenergan Tubex, but it is an example that's going to be used for illustration as to what generally a Tubex is. It's not offered as the Phenergan Tubex.

MR. O'ROURKE: No objection.

MR. RUBIN: And Exhibit 24 are two ampules or little bottles of promethazine. One is 50 milligrams, and one is 25 milligrams for purposes of illustrating another point in his testimony about how the product is distributed, and [87] it's not claimed that this was used on that date. It's for illustration.

MR. O'ROURKE: No objection.

THE COURT: All right. Twenty-three, 24, 25, and 26 are all admitted.

Q Okay. Getting—done with the housekeeping. Why don't you explain what happened starting with the Tubex first perhaps?

A Illustrate what the Tubex is. Tubex is a preloaded cylinder of a medication which, if it was used to inject with its needle, would be put in a—usually a metal, maybe a plastic, apparatus. It screws on—the plunger screws onto this little screw in the back, a rubber plunger that you can then push the solution as a shot down the barrel. So the Tubex by itself can't function. It goes into a mechanical apparatus. So the Tubex structure by itself cannot be used for an injection. It has to be put into an apparatus. Some of the apparatus might be metal or plastic and they're used to push down the plunger mechanism to make this into an injection.

We don't have a Phenergan Tubex of either 50 or 25 because those are no longer manufactured as I un-

derstand it. So this is another company's Tubex, [88] but it illustrates what Tubex is.

Q Okay. Is there writing on this barrel of the Tubex?

A This is a different medicine and there's the writing that tells about its concentration, its dose, its strength, and it says "For IM use only."

Q Now, that's—

A And a date for the drug outdating and serial number for the drug batch.

Q Now, what happened in this case was the contents of that Tubex was transferred into a syringe, right?

A The contents of two Tubexes. This product, Phenergan, came in two sizes of Tubex. That's all we had in our office at the time were these Tubexes. One would be 50 milligrams in one cc and would say "For IM use only."

Q Let me make sure the jury understands. I'm going to circulate this. It's capped and what—what you're saying is the Tubex for Phenergan has one cc in it?

A Yes, and one strength of it is 50 milligrams in that cc and that's labeled on—the barrel was labeled when it was manufactured "For IM use only," or words very similar to that.

[89] Q How many cc's—this is a Tubex of how many cc's?

A I'll have to look at it to see, probably got marks on the barrel. This has two cc's in it because if you let the air bubble go up, you've got two cc's of liquid.

Q So the Tubex with Phenergan was half that size?

A Half of this volume.

Q And did the Tubex have any writing on it for the Phenergan?

A The Tubex 50 milligrams in one cc I do clearly recall said "For IM use only."

Q What's that mean?

A For intramuscular, shot in the muscle as opposed to IV use only. I'm not certain that the 25 milligrams in one cc, which we used, said IM or IV. I know that it could be used either way, but I don't know if that was on the barrel or not.

Q Okay. So what happens next?

A So Jessica requested a nurse to get her the Phenergan and the nurse would transfer the contents of two 25 milligram—

Q Keep your voice up.

A —per one cc Tubex cartridges into a [90] single three cc syringe with a locking mechanism on the front so that it could be hooked onto the IV infusion device. She's got two in one so-to-speak. The nurse could draw that up in a number of ways. I think in this instance she pierced through the rubber in the back of the Tubex and drew it into the syringe.

Q Wait a second. So this syringe has three cc's or cubic centimeters of—

A Space.

Q —space. And what you do is you take two of those one cc Tubexes and load this up two-thirds full?

A That's correct.

Q Okay. Now, you have your cc—your syringe full of Phenergan, right?

A And she has some normal saline, salt water, and she has some Demerol.

Q This is sterile water?

A We would use saline and it would be drawn up. The top would come up and that would be drawn up in another syringe and she would have Demerol—in this case there was a 50 and a 25 vial used—drawn up into one cc syringe, so she's got three syringes lined up.

[91] Q Okay. So now she's got her three syringes all lined up with 2 cc's of Phenergan in the syringe; which is she going to inject first?

A She's going to put in the Phenergan first.

Q Okay.

A So she's—everybody has probably had their blood drawn at some time. Arm tied with elastic which has the venous blood not go up and shuts off the vein. So she would tie up Diana's arm in order to make the vein more prominent, she would probably try to not only see it, but you can tap on a vein. It's got a different feel than tissue, and locate the vein. She would wipe off the site with alcohol and get out this—this is called a butterfly infusion set. I don't know if we want to open that. We've got a different—another one here that's open. And these have a clear plastic tube connected. You can take off the device that closes that space, and then this would lock onto the syringe when ready.

Q Go ahead.

A So before—so she would take off this little cover and use these wings to hold the needle so that she could go into this vein and by—

[92] Q Excuse me.

A —by having the wings, I planned to keep this needle quite superficial, get under the skin—does feel a lot like skin—and then into the vein. You can then see some blood come back into this tube, sometimes it fills very much on its own, sometimes you have to draw back a little bit, and you see the blood come in. You can then make adjustment as to certainly whether that was dark, venous blood—you can see in this tube whether there were was blood that's dark as venous blood is or bright red as arterial blood should be. You might have to draw back a little to get the blood flow all the way back here. Arterial blood should be bright red and arterial blood sometimes will come back under more pressure. Venous blood should be darker. Sometimes you have to draw it and come back a certain distance—draw back to pull blood back into the catheter.

So this is an open system. She's in the vein, she's drawn her blood back, she takes off the tourniquet so that the blood can flow, the blood's moving through the vein, and she's got her three cc syringe with a blocking mechanism that locks on there, and then she slowly pushes that in. She's [93] got two cc's. She's got to take at least two minutes to put that in because the drug circular said you don't want to put more 25 milligrams a minute, and this is 25 milligrams in each of two separate cc's in this syringe.

So having done that, she can then unlock the syringe, put on her salt water so-to-speak, and wash that drug through. She's then got another syringe and she can put in her Demerol IV and she might begin to wash

that through, get the whole dose into the patient, not leaving some in the tube. Then she would normally put an alcohol—a cotton gauze over the site and pull out her IV. And hope it pulls out and stop and not bleed. I'm supposed to recap needles, but I don't think an eggplant will give me any trouble. So that's—that's the way it's done.

I would like to contrast that if I could to—

Q Could I ask you—the next question is there's another method of administering this or any other drug intravenously, right?

A There's also a third method I want to talk about quickly if I could. One could also take a drug, load it up into a syringe, push it into the [94] vein. And—as this one did—and then push the drug in. The drug circular makes note of the difficulty of the blood pushing back against the—the plunger. In the old days, which precedes most of us, there were glass syringes with glass apparatus which would move more easily and physicians were used to thinking if I got into an artery, it would push back and fill this thing on its own.

Q That's because the pressure in the artery will actually push it in?

A Push it open because these are not as slick, will not move as smoothly. That's not something to rely on. If you're going into the arm with this, you have not as much success as being superficial as you do here. The reason for being superficial is that veins are superficial and normally the arteries are deeper below what's called fascia, kind of tissue layer down in the muscle further away. So we elect not to use direct main linings so-to-speak with a syringe.

Q Is the butterfly system that you have described, do you use that in your practice or have you used this in your practice for all kinds of drugs?

[95] A Various drugs and for many years also it was used in the emergency room, no question about that, this same time period so it's—you call butterfly infusion sets.

Q What is the other method, which we will refer to as a free-flowing IV? Why don't we try and put these in the bag so that—

A Did the Tubex come back?

JUROR ONE: It's right here.

A So another way—a third way that one could use would be to introduce—probably set up hanging up on a hook—this little bag is very little, but you've seen IV bags that are bigger. They used to be bottles and this is this neutral saline which is not saltier or less salty than the body. So it neither adds water or pickles the tissue that it goes through. That would be set up with a—most people probably visited somebody in the hospital and seen this—an apparatus that would pierce the bag, the fluid would be run down, turn-off valve, run down and fill up this tube. This will be up in the air. This will be in it and you would have some dripping in here. The drops drop through and you can cont the drops and calculate the amount of the fluid that's going in. [96] This tube would be all filled up with this fluid. And these can be rigged to—could be rigged with butterflies, but would normally be hooked up with a device that is put into the patient like the needle like we spoke about, but then you can fill out this rigid obturator and that leaves this flexible catheter in the vein.

Q So there's a needle on here that you put into the vein, you take the needle out?

A And it leaves a sheath.

Q And this is just plastic. And that sheath is called a what? Catheter?

A A flexible catheter perhaps.

Q And where is that?

A That's in the vein and it's poking outside of the skin and has a little connector on the end so it can connect to this IV fluid. The fluid would then be running and one could inject their medication, Phenergan, Demerol, any other medication into a port in this IV and slowly put it in while the IV is running. The IV is dripping, the fluid is running through this at whatever rate and the medication can be introduced into the IV. You could either clamp off the IV, just pinch it and push sort of straight medicine with a little [97] dilution here or could have it run together, slowly push it in. This would afford a little dilution, but more affords the safety of not piercing back through the vein.

Q Why don't you explain in a little more detail, is this use of a free-flowing IV—put that back together before someone gets stuck, like me. Does this use of a free-flowing IV provide any additional margin of safety or assurance that what you're trying to put into a vein will go into a vein and not go into an artery or go into the tissue and then bathe the artery?

A I think that it would because if one were in an artery, this IV would not drip well and it might even have some slow flow of arterial blood back in because arterial pressure would push up against the gravity drip of the IV.

Q So if it's dropping into a vein, the pressure in the vein wouldn't stop the drip?

A You have to have untied your elastic, but it can drip at quite a fast rate.

Q And if it's in an artery—

A It would run against arterial cystolic pressure, 120, 140, and it would tend to run poorly. And you read the script of this happening [98] where blood comes back up into the IV set. I read an article where an anesthesiologist notices during surgery that whoops, we must be in an artery because there's blood coming back up into our IV infusion back and tubing.

Q What if you're inadvertently not in an artery but into the tissue outside the vein?

A Then you're going to—IV is going to run for awhile, but it's not in a conduit, it's in kind of a closed space. And once it's swelled up, it runs some cc's into tissue under your skin and amongst all the structures there, it's going to make it—we can call it a bubble, a fluid, but then it's going to be having a harder time to flow and it's not going to flow correctly.

Q If you were to set up this free-flowing IV and let it run for a couple or three minutes what measure of protection would you have against what happened in this case?

A You would have a lot more assurance that you were in the vein and not outside of the vein. And I think—I think it's clear that the injury could happen whether you were outside of the vein and in an artery or outside the vein around an artery.

[99] Q Okay. Why don't you take your seat. Have you reviewed the product information or insert that's Exhibit 1?

A Yes.

Q Okay.

A Not today, but previously.

Q Is the method—had you reviewed it before the incident?

A Absolutely.

Q And have you read it several times since?

A Absolutely.

Q Is the method that was used with the butterfly infusion set with that small butterfly consistent and appropriate under the instructions provided with a product by Wyeth?

A Yes.

Q Why?

A It's a functioning IV infusion set. The name of it is IV infusion set.

Q And is there anything else in the instructions with respect to dosage or needles that would further support a conclusion that it's consistent?

A Um, the product is said to be safe and [100] effective. I think it is in IV, and it's listed as appropriate to give it at 25 milligrams per minute, which can only be given 25 milligrams per minute, it shouldn't go faster. That has to be put in by IV push, slow IV push, as opposed to say being in a bag and dripped over a couple of hours. So that rate implies that or tells you that you can put in 25 milligrams every minute safely

into a vein. I have to say that in retrospect I think we're wiser about this and I must wonder why the 50 is labeled for IM only, the 50 milligram concentration per cc, but the 25 milligram is not labeled for IM only in that it turns out to be extremely caustic as it is.

Q What about the fact that the instructions appear to mention the use of—referred to plungers and rigid needles? Does that imply that you could give it IV push?

A It does, that you would be using it IV push. In the case of the plunger parts, I think we got around that by having the tube that could fill on its own. But by—certainly by talking plungers and rigid needles, that's the way you do it, to push it with the plunger.

Q Is the use of the butterfly infusion set, was it used in the—in April of 2000 [101] commonly to administer Phenergan?

A Yes.

Q Intravenously?

A Yes. We checked that. It was occurring at hospital in Bennington; certainly occurring in our patients seen at our emergency room. Several doctors in the hospital, when this came to their attention, came and told me that this scared the devil out of them because they—

MR. O'ROURKE: We object to that. That's certainly hearsay.

THE COURT: Yeah. I'll sustain the objection as to what people told you.

Q So the answer is yes, it was used at other facilities?

A Absolutely.

Q And why don't you always—you were aware of the risks of arterial—of this getting into an artery, right?

A Yes.

Q And they do talk about that?

A They talk about it in their package insert.

Q Yeah. Well, why then wouldn't you and others always use one of those free-flowing or [102] hanging IV systems?

A In retrospect I wish we had. At that time for this and a number of other drugs you're just going to be in the vein for two, three, five minutes and pull out the needle and be done. And so that the need for hanging a bag of IV fluid was less apparent. I also think that the idea of infiltrating was clearer to us. This is getting the material out of the vein. It might leak out of a hole in the vein or you might pierce the vein in the back and have some flow out around the vein and therefore bathe the artery. Concerned about local—in the anterior part of the arm tissue injury was clear to us. The idea that one would get into an artery seemed quite foreign to us and to everyone we spoke with because we were using the superficial approach with the butterfly needle.

As it turns out, and I'll tell you that none of—no one of us recognized this possibility—there is this aberrant artery business. It's not mentioned in the insert. They talk about arteries close by or something, but the aberrant artery—I think three percent on the side that Diana's injection was done on, maybe 14 percent on the opposite side of the arm, is just not something [103] that anybody is aware of. I did a literature search when we were trying to figure out what to do to help

Diana and I couldn't find any mention of any of this in a 25 year computer search.

We subsequently found articles by using the Dartmouth medical librarian to look further back than the computer could look for us. And we found some articles from 1968, '69, '70 talking about these injuries and aberrant arteries.

Q What is an aberrant artery? As it relates to this case?

A There's the usual anatomy where the veins are superficial, and the arteries are deeper, down in the muscle or below what's called fascia, kind of a glistening layer of something over the muscle, tissue—fibrous tissue. Aberrant arteries are arteries that are not in their usual location. So they can be both where you're not expecting them, and superficial, meaning closer to the skin, and therefore closer to the vein that you're targeting for your injection. We've learned that you don't have to be in the artery, you could soak the artery or surround the artery with fluid that got out of the vein by one way or another leaking out of the vein or if you counterpuncture **[104]** the vein all the way through, and that could injure the artery, probably soak into the artery. It could also injure the little nerves that travel with the artery that direct the artery to dilate or constrict. So it can damage the sympathetic nerve that run the dilatation or contraction of the artery. It can soak into the artery even if you didn't pierce the artery.

Q I'm going to get back to the insert in a minute, but can you tell us what happened to Diana's arm?

A Um, she came back in that afternoon with this discolored, painful—her arm was sort of bluish and

blanching and it was—the vessels were sometimes dilating and sometimes contracting. She had areas that would be bluish or white. Other times it would be rosy red and we—

Q Was there pain?

A Oh, there was pain. She ended up in this interval, the next two and a half or so weeks, taking quite a lot of narcotic pain relievers, both pills and patches that absorb through the skin and sometimes injections. So we spent about two and a half weeks trying to rescue her arm. And actually for a long time we thought we were succeeding. We

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[107] qualifications, and with a Doplar sound machine that uses a sound like radar, couldn't find any pulses below I think the point of splitting her brachial artery into her two forearm arteries. She also saw Dr. Michael Mason, who puts in a block to her arm to block the sympathetics hoping to dilate her vessels and to help her pain. And despite all of that, in our local hospital we were clearly failing, her limb was at risk.

We transferred her down by making arrangements by telephone to Dr. Jack Cronenwett down at Dartmouth-Hitchcock Medical Center and Dr. Curran did an immediate quick discharge note, some typed pages to send down with her, and she transferred down there.

Q Was the subsequent amputations that she had the direct result of the injection of Phenergan to her arm?

A Absolutely.

Q Do you know what the actual mechanism was that started this spasming and the subsequent gangrene?

A We know that the drug is extremely caustic. We know that if it it gets in the artery, it causes inflammation and spasming and eventually [108] an obliteration so they're gone to small vessels, capillaries and little arterioles, and therefore, one could have this bad looking, poor circulation in the fingers and still have pulses say at the wrist, for example. You apparently can get the same thing, from what we read, by extravating the fluid, having it go outside the vein and bathe the artery by injuring the artery. It may soak into the artery and go downstream or it may cause its trouble at the local.

She went down to Hanover. We didn't yet know all that was going to happen. And Dr. Curran had actually thought that maybe she had a local blockage of her artery in her arm from the vessel getting inflamed and narrowing down and getting a clot in it. So we thought she might be able to have the clot fished out and that section of artery repaired. I should say that we also during the course of this two and a half weeks got an ultrasound of her arm seeing if the vein had a blood clot in it because her arm was quite swollen. So in Hanover at Dartmouth-Hitchcock Medical Center, as I understand it, they—

Q I actually will talk to—I just wanted you to stop when your care stopped. When was the [109] transfer?

A We transferred her down to Jack Cronenwett at Dartmouth-Hitchcock.

Q What is the relationship between feeling pain and the damage that's done that causes this problem to start?

A I think in reading now that if you have severe pain down the limb, let's call it, that the damage is done at that point. No one we consulted in the course of this said look, you guys are not going to succeed at this. They all suggested what we were doing. But as we read now, and it may be that this was irreversible from that moment, that when the bad pain happens, if there's bad pain, the damage has been kicked off.

Q I think you started to answer this question a little earlier, but I wanted to ask you how this tragedy could have occured with the use of a butterfly infusion set? What were the mechanics—physiological mechanics that probably caused this to happen? You talked about the presence of aberrant arteries. Anything else?

A Well, I think that through inadvertance or an error this material got out of the vein either because the needle went through the vein and [110] was beyond it, counter puncture, make two holes and put it out in the tissue around the artery, or it leaked out of the vein through the hole that the needle was making, or it got actually into an artery. It might have been in the artery for a brief time and then when Jessica checked her position, it wasn't in the vein because the needle can make a little bit of motion. So then we could have had an aberrant artery near the vein that could have gotten bathed in or punctured and percolated with this medication. Or perhaps without even having an aberrant artery, the material could be in the arm, get around the artery enough to do this damage.

Q Is there any way to treat this effectively once it starts? Despite the reference, what does the literature say about that?

A We now know that one's quite apt to fail and there may be nothing that will succeed in this case. I

read some cases where similar treatments to what we did succeeded in saving somebody's limb. We don't know how much they got into their vein or around their vein. And I read some—a number of cases where everything failed.

Q Do you believe this product, Phenergan, [111] is safe with the instructions as they were written in Exhibit 1 in 2000?

A I do not.

Q Why not?

A I think that it—it does have some warnings, there is no question of that. But I think that the foreseeable accident or inadvertence is common enough that I think the drug should be labeled "Not for IV use." If it were going to be used IV, I think that it should say that it has to be in a running—established IV running at a certain rate. I'm not sure that I would buy the concept that if it were diluted, it would be safer, so I'm not thinking the IV would dilute it significantly, but it might better assure the IV route. But even then, you know, we're gaining 15 minutes of comfort. We're gaining some quicker relief. Seeing what happened and realizing it can happen in careful, experienced hands makes me think that this drug is inadequately warned, and frankly, we will not use it IV again diluted or in a running IV. We won't let that happen at the hospital to our patients and I don't think it should be used IV. I think it should be for IM and other uses, but not IV.

* * *

[116] IV. It would have been IM. If we used it, Diana would not be in the position she's in with the loss of her arm and we would not be here.

Q If this said use a—if you're going to use it IV, use a free-flowing hanging IV system, do you have an opinion as to whether this tragedy would have happened?

A I think it would be extremely reduced in likelihood. I don't want to say it would be impossible, but the running IV would have given us more assurance of being in the vein.

Q I just have one more brief area of questions. I think we're going to hear from Mr. O'Rourke you wrote a letter to Diana at some point after this tragedy happened?

A I did.

Q And without getting into the particular details, what did you—what were you doing when you wrote this letter? Why did you write this letter?

A Diana and I had been friends for 20 plus years and I wanted to communicate to her my personal feeling of regret and remorse for what had happened. Frankly, it did me perhaps more good than her to get it off my chest.

* * *

[159] to go home.

Q Doctor, does IV Demerol provide quicker relief than IM Demerol?

A Yes. Demerol IM can be erratically absorbed. Erratically—not just slower, it's less reliable in terms of the absorption curve so-to-speak.

Q All right. And how about Phenergan? Does IV Phenergan provide a quicker relief than IM?

A Yes, sir. It provides quicker relief probably by 15 or 20 minutes.

Q Okay. Doctor, we talked about—or you talked this morning about aberrant arteries?

A Yes, sir.

Q Under your direct examination. And Doctor, I'm going to show you what I've had marked as Defendant's E for identification, and it's an article from Moore & Daly on anatomy and ask you whether or not that document—and I have the book here—that's a portion of the article—whether that contains some information on aberrant arteries in the arm?

A I should tell you that this is the first day I've seen this sheet. It does say—and it's highlighted—that there's information—

* * *

[164] Q Well, Doctor, so we won't have to ask you to come back here another time, let's assume that we're going to have evidence in this case, and evidence from the plaintiff herself, Diana Levine, that she yelled and she screamed that she was in pain; assume that's going to be in evidence, do you agree at that point that Jessica should have stopped injecting the medication?

A If she screamed out in pain?

Q Yes.

A That she had pain, I think that she should stop giving the medication. And I think from what we now know, that the damage to her arm would have then been already done.

Q All right. Now, you say you now know that, Doctor, do you know how much—how many cc's had

been injected into Diana's arm at the time that she screamed or yelled in pain?

A I don't know how much of that two cc's had gone in.

Q Have you had any scientific studies done to determine how much is needed into an artery before it's an irreversible situation?

A I read an article that said—in the peer-reviewed journal—that said that a woman in

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[183] A I found it in a like location, "For IM or IV injection."

Q Do you know of any reason or studies which support the use of this drug intramuscularly only for the 50, but for both ways for the 25?

A No, I have to say that—we've not been able to find anything. I don't know if any of your other witnesses have or not. I haven't been able to find any studies to say it should be safer at 25 per cc as opposed to 50 per cc. And I have to say that in retrospect, it's strange to me that one is precluded from IV use and the other is allowed for IV use.

Q Mr. O'Rourke asked you about the changes to the policies that are used at the emergency department up at the hospital. Now—after you wrote your letter saying that this was a dangerous drug. And could you tell us how they changed exactly? Do they—

A I think they changed before I wrote the letter. What I did is went and spoke to the E.R. director and I think before I wrote the letter to the medical staff as a whole they changed to require running IV and a ten to one dilution.

Q So what they did was they said they got [184] to use this system here?

A Yes.

Q Because it's safer?

A And dilute the drug.

Q Yeah, but this system because it's apparently safer?

A Safer in terms of route.

Q And in addition to that, they wanted or required that what comes in that Tubex be diluted ten to one or nine to one?

A Yes.

Q Knowing what you now know, do you think it's appropriate—it was appropriate for Diana to have received an intravenous butterfly injection of this drug? Phenergan?

A Absolutely not.

Q Why not?

A She should not have received it. She should not have received it because it's more unsafe than we knew and the enormous risk—even though the odds might be small in any one instance—is nowhere near offset by the small gain of 15 or 20 minutes less vomiting or nausea. I don't think the drug should be available IV and I wish that it hadn't been and then we wouldn't have used [185] it.

Q Now, when they asked you to read your letter of apology to Diana, the implication was that your testimony here today is somehow affected by the fact that

a claim was made against the Health Center and resolved. Is that the case?

A I'm not sure what the implications of those questions were. The case was made against the Health Center, resolved, and we had no deals. That I didn't even know this court case was going to come up. And this is nothing to do with that court case as far as I understand. We made—this was not a part of that process and I didn't know this was going to happen. And my being here today has nothing to do with that court case. We had some responsibility and we took it.

Also I don't know quite how the letter is supposed to reflect on my motives today. I back every word of that letter and I would say them with as much emphasis today as the day that I wrote it. But that does not make me come to court about this matter. I wanted to get the facts on the table about this drug. I don't think it should be available IV. I think that there were things we learned since this injury that made me understand

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[187] that says gee, why can't I give it IV? I do it all the time. We tell them absolutely you can't. I think it should be like Vistral and not be allowed to be used IV.

Q Other doctors at the Central Vermont Hospital use it IV?

A Yes, they do.

Q About the letter, I don't think anyone is intending to impugn your integrity, your abilities as a doctor, your abilities as a physician, your treatment of Diana, but the letter indicates you said that you accept responsibility for what happened to Diana, isn't that so?

A Yes, it does.

Q And what responsibility do you accept? I mean what did you do wrong?

A We chose this drug. We administered it as directed in the package insert. And that's part of our responsibility. We had to make this choice. It's our position there is a drug company, there is a patient, we're in between. We're supposed to have a cooperative, collegial, mutually helpful to our patients relationship. And in this instance we chose and used that drug in good conscience. I think that Jessica appropriately used it, although [188] I now knowing what I know now, I think we shouldn't have used it. Diana shouldn't have gotten it, and the—I think that in this case the trust relationship between the drug company and myself as a medical practitioner broke down. We should have had more warnings about this. If cases were being reported to Wyeth, we should have had the representatives who come and sell us drugs should have come and told us about this problem. It shouldn't have been submerged in the literature for 30 years. And the instructions and warnings and so forth as they're printed I think are inadequate, insufficient. I don't think the drug should be used IV.

So I'm responsible for having used what I believe now is a product that shouldn't have been available to me to use. I'm also responsible for any error that Jessica made, whether it's inadvertance or accident. I'm responsible to the extent if we could have found any solution for Diana's injury, I'm responsible for our not having—maybe there was no solution, but we did our best to find it. So I wouldn't change a jot, as I said, of that letter, but that doesn't mean that there's no responsibility for Wyeth. There is some

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[Testimony of Dr. Harold David Green]

[194] A Yes, I am.

Q Okay. What is the difference between the free-flowing system and the butterfly system from your perspective in terms of safety?

A The free-flowing system is where you will hang an IV bag full of solution usually saltwater or dextrose, sugar water, and that is dripped into usually a catheter that we put into a vein rather than a rigid needle. So the catheter is introduced with a needle and—with a needle poke—but then over the needle is slid a soft rubber catheter, or some other polymer other than rubber, and the rubber catheter stays in the vein. Being soft and plastic, it doesn't penetrate the vein anymore. Once it's introduced, it stays there. And then that's hooked up to the intravenous tubing to an IV and the fluid is dripped through that.

Q This is in evidence. The jury took a look at this. I can't take it apart. You do it. Okay. Now the jury saw that this morning the catheter to which your referring.

A Yes.

Q And the needle comes off?

A Right. So there is a needle in the [195] center with a soft catheter on the outside. Once you penetrate the vein, then the catheter is slid into the vein and then this needle is hooked up to the intravenous tubing which is hooked up to an IV bag of solution.

Q Does this system of using a free-flowing IV protect the patients from either an arterial injection or the infiltration of the drug outside the vein and into the tissue?

A Yes. This technique almost precludes an intra-arterial injection if the IV is running. If it's adequately running. It can still extravasate sometimes, but usually when it extravasates it occurs immediately.

Q What is extravasate?

A Well, when this needle enters a vein and the catheter is then slipped into the vein and the needle is pulled out, then you start running the solution in. If the needle went through the vein in two places, or if it went —just sort of hit the vein and then came back out and the catheter actually sorts of goes through the vein or out the back wall, now the catheter is not totally in the vein, as you inject—as the infusion, the fluid drips in, it will extravasate which means that it **[196]** will end up outside of the vein so that happens almost immediately. As soon as the IV is started, you see it dripping and if it is not in a vein, it has either a lot of resistance so that the IV will not run or the nurse or whoever is doing it will notice a little bit of pain oftentimes and some swelling and then as the swelling gets larger at some point the intravenous will stop.

So at the very beginning of the intravenous first setup, this has a risk of extravasation, that is fluid going outside the vein. But once it's running, once the catheter is in a vein, this catheter is longer than the butterfly, it's soft, it isn't—even if the patient moves, it isn't going to puncture the vein anymore. There's no sharp object in there. So it's very rare for these to extravasate after everything has been established when it's running.

In addition, because the intravenous—you can calculate sort of simple physics—that the blood pressure in our arteries, as you all know, is typically 120 over 80 is the typical blood pressure. That's a pretty high blood

pressure. That's enough to push a column of water up about five or six feet. So if you put a needle in an [197] artery, and you hooked it up to water, it would push that water five or six feet up. And that's where the IV is hung. It's hung, you know, about four feet up or even less, three and four feet. So if there's—if it's in an artery, the blood from the artery will go up into the catheter and into the IV rather than the IV fluid traveling into the artery.

So a running intravenous, once it's established, is a far safer means of administering any medication to prevent extravasation and to prevent arterial injury or arterial injection.

Q So if you let that saline flow for a few minutes, you would be pretty well assured that it was in the right place?

A Yes.

Q Before you put the medicine in?

A Correct.

Q How often do you use the direct infusion or the free-flowing system, not with Phenergan, but generally?

A Most of the time we're administering fluids to patients and so when people are vomiting, they come to the emergency room, they'll be dehydrated as well, so in that case we want to give [198] them the fluid so we establish the intravenous, and I would say that's the majority of cases. We might inject some medication through the free-flowing intravenous solution as well as giving them the solution itself. So the majority of the time we're using a free-flowing hanging IV system.

Q But you also have used the other?

A Yes.

Q And you're a pharmacist, right?

A Yes.

Q Most of us know what a pharmacist is, but how does it relate to what you're here to talk about?

A Well, as a pharmacist, I was trained to understand pharmacology of drugs. That is how they work and also the process by which drugs are approved by the government for use in the country and the properties that are involved in that processes. With my pharmacy degree I've continued, as I said, to maintain my registration in pharmacy and at the previous hospital that I was at, as well as at Tufts New England Medical Center, I'm the chairman of the pharmacy committee.

Q What is the pharmacy committee's role at this—at your hospital?

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[208] guess briefly is better than generally—what your understanding of how the Phenergan was administered to Diana Levine in this case. We've heard testimony a few minutes ago about that so just tell us what you understand.

A My understanding is that the nurse—one of the nurses at the Health Center took two 25 milligrams per ml, and cc is the same, Tubex syringes, took the drug out of them, and injected them into the barrel of a standard three cc syringe.

Q Is there one in there? Three cc syringe in there?

A Yes. And then while she was doing that, or about that time Jessica Fisch had inserted the butterfly

into this part of the arm, the antecubital space, into a vein. And got back flow, got blood return. And then Jessica took the syringe with the 50 milligrams, now two cc's of Phenergan and hooked it up to the tubing of the butterfly and injected that over about two minutes.

Q And how—how would you determine that this system is functioning properly? You're using that infusion set. You've explained how you would determine if it were a free-flowing system, but how [209] do you determine that that system is functioning properly before you put in the medicine?

A Well, it's a little bit harder to be as certain with this system. What one does is when you put the butterfly in and you get return of blood, if youo're in an artery, the blood shoots out and is bright red. You're in a vein, the blood—you get blood return, and if you're not in anything, you don't get any blood or just a quick flash and that's all. So to determine if it's in a vein where it should be, you get back sort of darker red blood not under high pressure.

Q Is it possible to be fooled with this system?

A Yes.

Q How's that happen?

A Well, first of all, because you're using a needle and the needle stays—well, a assuming put in the vein to begin with, if you're in the vein, the patient moves over a couple of minutes, we move a little bit and it may puncture the back side of the vein. And if there is an artery that's very superficial, very close to the surface, you can puncture an artery or it can just extravasate. It can just go outside of the vein and then bathe [210] an artery that's nearby. So the fact that you have a sharp object, a sharp, rigid needle in the vein is a prob-

lem and then you don't have the safety features of a running intravenous that would stop if you extravasated and you have a catheter instead of a sharp needle in a vein. So it's just generally not as safe. We frankly generally don't like to administer medication this way. If the patient needs an IV, we would much rather have an IV running, just a more secure way.

THE COURT: Mr. Rubin, this is probably a good time to take ten minutes.

MR. RUBIN: Yes, sir.

THE COURT: Let's do it. So about quarter after we'll all get back together. Everybody can stretch.

(Court recessed from 3:03 p.m. to 3:13 p.m.)

MR. RUBIN: I'm sorry, your Honor. I didn't realize—

THE COURT: Not a bit, no, no, no. It's fine.

Q (By Mr. Rubin) What is your understanding, Dr. Green, of what actually happened to caustic the injury in this case?

A My understanding is that when the [211] Phenergan was injected, some of it or perhaps all of it escaped from the vein. It either went through the other side and it either bathed an artery, that is it extravasated out of the vein, or it actually entered an artery directly. I don't think anyone can tell. This type of thing has been reported in either case where there's extravasation of the Phenergan apparently close to an artery or direct injection into an artery.

Q And could this have been caused by the Demerol?

A No.

Q Why not?

A Demerol is frequently given with Phenergan and as a pain reliever, however, it's actually been studied with Demerol. There was a study done in I believe it was in the late '60s where Demerol was injected along with other substances into the veins of animals and it was determined that Demerol doesn't caustic that effect that other drugs like Vistral can caustic this effect and Phenergan.

Q And what is the mechanism by which once it's in the artery the arm goes into gspasming and ultimately the tissue dies?

[212] A The—I think there's not a complete understanding of how this happened. However Phenergan in a general sense and some other drugs like Vistral are irritants to the artery. They somehow damage the internal lining of the arteries especially the tiny arteries. As the artery goes down the extremity, they get—they branch out and they get smaller and smaller and apparently these very small arteries become damaged. There's also some degree of gspasming that the artery goes in as an irritation just by being irritated or by damaging the nerves around the artery, that the artery has little muscles in its walls and it constricts, so you get a combination of constriction of the blood vessel, the larger blood vessel, and then damage to the blood vessels—the smaller blood vessels further downstream. And that damage actually then continues to produce problems because the blood gets stagnant again. It doesn't flow through the arteries so the blood starts to clot. So it's a combination of gspasming, inflammation and clotting. And then the very tiny blood vessel actually starts to leak fluid and fluid accumulates around the arteries, and it's a combination of a number of

things which is probably [213] why there isn't any good, simple, straightforward treatments, even though many different things have been tried such as anticoagulants, nerve blocks to allow the blood vessels to dilate and medications for dilation, and even drugs that break up clots. And there isn't anything that clearly works probably because it's a multitude of different things that are happening to the arteries at the same time.

Q Is it foreseeable that the use of a butterfly infusion set like the one used here will result in some cases this will happen?

A Yes.

Q And why is that?

A Um, directly injecting a medication is not a process that's a hundred percent foolproof no matter how much experience a clinician has, no matter how much care they take, there will be sometime when they will be near an artery and not be aware of it or extravasate the medication. That's just the nature of direct intravenous injection. It's not a foolproof process regardless of the amount of care that's taken by the clinician. So this is foreseeable, that if it's permitted, if it's recommended that direct arterial [214] injection—I'm sorry—direct injection of medication into a vein or attempted into a vein is just foreseeable that at some point in time you do this enough times and the fluid medication will either extravasate or be inadvertantly be put into an artery.

Q Is there anything in the literature or other information that you've reviewed to show that that reveals that this has happened before other than just that it's likely to happen as you described it?

A Yes.

MR. HOFFMAN: Pursuant to what we discussed in chambers, I have an objection to this evidence.

THE COURT: Understand. Overruled and you may continue.

A Yes. There's information in the literature and there are reports of this happening with 25 milligrams of Phenergan or less. It's happened with 50 as well. All by direct injection and generally by nobody trying to get into a vein, but, you know, most cases—

Q Nobody trying to get into an artery you mean?

* * *

[216] the—in those reports as it relates to the kind of event that occurred in an administration similar to the one that happened in this case with a direct infusion?

A Yes. The reports indicated, along with the files from Wyeth, plus what's in the literature, that since the late 1960s there have been at least 20 cases where Phenergan has caused an amputation. There have been many more cases where the person's arm or hand or finger has turned blue for a while and luckily no amputation occured.

Q We're talking only about direct injection here, not any other method of injection?

A That's correct.

Q Okay. Is there anything in the actual product information itself that says that this can happen?

A Yes.

Q And what's that?

A Under the section that says Inadvertent Intra-arterial Injection. Would you like me to read part of it?

Q No, I think Mr. O'Rourke read that, but it's in the literature itself that there are reports to that effect?

[217] A Yes.

Q You may have already just answered this question, but is it foreseeable that this will happen with the butterfly as opposed to the free-flowing IV? I think you may have answered that question.

A Yes. It's theoretically possible to happen with the free-flowing IV, but it's harder to do and it's almost expected that at some point in time it will definitely happen with the butterfly setup.

Q Okay. Is there anything in the literature about the presence of abberant arteries?

A Yes.

Q That's relevant to your opinion?

A Yes.

Q What is that?

A The literature says that there are blood vessels, arteries in the upper extremity that are aberrant. That is they either don't exist in the majority of people or they exist but they take a different course. And that's important because the artery, the main artery in this part of the arm, the antecubital fossa that we call it area, that artery is called the brachial artery and it is [218] deep, very deep. And sometimes we actually do try to penetrate that and we usually need a rather long needle to go straight in. That's the usual course of that artery. But sometimes the artery actually branches up

higher and takes two branches that come down, become superficial. So they're right underneath the veins or at the same level as the veins. So it can be abberant in the way the way the artery branches and its location or it can be just a separate branch that most people don't have that shows up. The incidence of the artery brancing early is about 13 percent of people and the extra artery, if you will, that's not there in most people is about three percent. So it happens a moderate number of times that that type of thing can occur.

Q Is it foreseeable that this will happen in a number of cases by a clinician making a mistake somehow?

A Well, it will occur even with a careful clinician because they will just be unable to determine whether their person has an abberant artery or whether they've actually penetrated through the vein and entered an artery with a butterfly set. You just can't tell at times.

* * *

[225] Q Now, Tubex syringe was not used in this case, a different kind of syringe was used. Does your opinion still stand?

A Yes.

Q Why?

A Again, it's the direct injection that's more important than whether a Tubex is used or not. Because by directly injecting medication into a vein or what you hope is a vein, someday someone will be outside the vein and they will not know it. They will not be aware or in the sense that's detectable, it's an error, a problem, and it will ust occur as certainly some accidents occur such as being struck by lightning. It will happen someday to somebody. And it's foreseeable.

Q Well, a little more foreseeable than lightning, right?

A Yes.

MR. HOFFMAN: Your Honor, I object. Side bar comment from counsel. It's argumentative.

Q Is it more foreseeable than a lightning strike?

THE COURT: All right, all right, I think we get the point.

MR. RUBIN: I'll withdraw the question.

* * *

[230] MR. RUBIN: We won't use that document.

Q Do you believe the warnings and instructions contained in the Wyeth product information were adequate to make the product safe?

A I do not.

Q Why not?

A I think the warnings and statements in the package insert by Wyeth, first of all, say that given intravenous Phenergan is well-tolerated, but not with some risk. I think the cases that I've seen and what happened here are certainly indications of more than some risk. And that that statement implies to the clinician that go ahead and use it, it's a pretty safe product, and go ahead and give it by direct intravenous injection. But they also say that intra-arterial injection, even though it isn't meant to be an intra-arterial injection, has happened from time to time. But it's still okay to use the drug by direct injection when it is clear that most clincians and the manufacturer know that there are safer ways of administering this drug than by direct injection such as by using a free-flowing IV.

In addition, the manufacturer has implied that the 50 milligram concentration is the unsafe [231] concentration to be injected intravenously, whereas the 25 milligram is safer. There is no information that backs that up. Certainly dilution may have some effect, that is the less concentrated solution might in fact be less dangerous, but there are cases of this happening with 25 milligrams or less and there's no study that's been done to support the 25 milligram per ml injection over one minute being safe.

Q Do you believe the language in the warning that's says that the veins and arteries are close to each other in the area where you're likely to inject it is sufficient to warn of probability or possibility of abberant arteries?

A No, I don't think that's sufficient. I teach medical students and, you know, we have anatomy usually in our first year of medical school and unless we become surgeons and become intimately involved with specific areas of anatomy, this isn't something that most clinicians would be aware of who use this type of a product. Give it to an obstetrician, he's not going to know or remember much about arm anatomy. Even if he learned about abberant arteries, he won't know very much. But an abberant artery is much different than an artery in [232] a vein being in proxiimity—I mean they were in proximity, but they're abberant. But warning a clincian that arteries are different in different people and you may not be aware of the fact that there's an artery right next to that vein that usually isn't there. Because what we do learn, most medical students and residents, learn how to do a blood gas, how to take blood from an artery at this point. And it's hard and it's deep and you can't—it's hard to feel. So that's what our experience is and I think the manufacturer should have clearly said

that abberant arteries can be present and you can't tell and you don't know which patient they're going to be, who you're going to find them in.

Q Now, that's the kind of alerting you of what can happen, but what about the instructions themselves? Do you think those are adequate on how to do it or how you can do it?

A Are you referring to the—

Q IV infusion set that's known to be functioning properly?

A Right. Well, that—that's inadequate in that I really feel that this drug is probably not safe for intravenous injection at all. There [233] isn't any need to use this drug intravenously and, as we know, Vistral, a product made by another drug company called Pfizer, the drug company voluntarily decided back in about 1970 not to allow Vistral to be used intravenously because of problems such as this, where people have got gangrene and amputations, and the manufacturer decided it just isn't a drug that's so important to be given intravenously that they decided in the package insert to say IM use only, no intravenous use.

So in the first sense, I believe this drug is not—there is no desperate need to recommend its use intravenously. And if it's used intravenously, then the manufacturer I think is obligated to tell the clinician what is the absolute safest way that this could be given intravenously? And that would be through a free-flowing IV, not through a functioning infusion set.

MR. HOFFMAN: Your Honor, pursuant to our discussion in chambers earlier, I have an objection to the evidence on Vistral.

THE COURT: Okay. I'll overrule the objection. But appreciate you bringing it up.

MR. HOFFMAN: Thank you, your Honor.

[234] Q Wyeth has said that there was a complaint of pain by Diana Levine when the IV was started and the medication went in. Do you have any opinion with respect to the fact that the company warns that you should stop when there's pain as to the outcome in this case?

A Yes, I do.

Q What is it?

A In my opinion once the patient experiences pain, that is an indication that the drug has damaged the artery. Arteries are not usually painful unless they've been injured. So presence of pain shows that a problem has occured. And there have been cases where the patient has complained of pain and injection immediately stopped and they've gone on to have necrosis and amputation. So I think there's nothing in the literature that says that once the pain occurs, once the probable intra-arterial or peri-arterial injection occurs, that there's anything that will prevent it from getting worse.

Q And what should have been in the instructions or the product information that would have prevented this from happening?

A Well, the best thing to have been in the [235] instructions was do not use our product intravenously. It should be for IM use only. That's the best thing. The next best thing would be to talk about aberrant arteries, to talk about using the medication only through a running IV, and it would have been best if the manufacturer had done studies to find a concentration that was

safe. So if they said take 25 milligrams and diluting it ten-fold or twenty-fold or fifty-fold, that when we do that in animals, we have don't see any problems and that would have been a very safe and easy thing for them to do. That they could have—if they found the concentration that was safe to have put in the literature.

MR. RUBIN: Thank you. Your witness.

Cross-Examination by Mr. Hoffman

Q Good afternoon, Dr. Green. I'm William Hoffman and we didn't meet until just on the break?

A Hello.

Q Is that correct?

A That's correct.

Q Dr. Green, in the United States who has the responsibility for deciding whether a drug should be available for marketing?

A The manufacturer of the drug with the [236] approval of the Food and Drug Administration.

Q Okay. And is it true that the FDA assesses the benefits and risks of a drug before it allows that drug on the market?

A It does today, but it didn't back in 1950.

Q Your testimony is that the United States Food and Drug Administration did not review the effectiveness and safety of Phenergan and approve it for marketing?

A The—now, I'm not a lawyer so I don't—I'm not—but this is my understanding, that the Food and Drug Administration, the Pure Food and Drug Act ini-

tially allowed the FDA to determine that drugs were safe. And that they were labeled properly that if the package said it had 25 milligrams of Phenergan, it had 25 milligrams of Phenergan, give or take a little, but it wasn't until much later that the Food and Drug Administration in a subsequent amendment to that Act was given the authority to determine that a drug was effective.

Q Do you know whether—do you know what a New Drug Application is?

A Yes.

* * *

[240] issue here is appropriate to use?

A Um, I've seen documents from the FDA to Wyeth and from Wyeth to the FDA stating that Wyeth's best thinking was that this medication, Phenergan Injection should only be administered through a running intravenous. And that the letters back and forth that I saw indicated that the FDA was in agreement with that. However, the final letter from FDA to Wyeth for some inexplicable reason says forget what we told you before, and we don't think—and just keep—keep the labeling the same.

Q So the answer to my question is yes, the FDA approved the form of the labeling that we've been talking about today, correct?

A I think somebody at the FDA made an administrative error and approved it, yes.

Q Did you talk to anybody at the FDA about this?

A No, but I read the several letters back and forth between Wyeth and the FDA.

Q Okay, and you read the label—the letter that said this labeling that you're using is appropriate, you may continue to use it? Correct?

A Um, words to that effect, yes.

[241] Q Okay. You've never worked for the FDA?

A That's correct.

Q You never consulted with them?

A About this case?

Q About this case.

A No, I just asked for reports that they had.

Q You've never worked in the development of a drug, have you?

A No, I haven't.

Q Never worked for a pharmaceutical company on labeling for a product?

A No, I haven't.

Q You're not an expert on FDA regulations, correct?

A That's correct.

Q You've testified that there should be no ability for physicians to use Phenergan intravenously in the United States, correct?

A Um, well, what I would say is that the manufacturer and the labeling should say for intramuscular use only.

Q Which would have the effect that doctors, unless they wanted to ignore the labeling, not to use it intravenously?

* * *

[246] Q But for the patients that you prescribed the medication, you believed that the benefits of using the therapy outweighed that risk?

A Yes, I did.

Q Now, let's talk about efficacy for a minute. You would agree with me that there are situations in which a patient is vomiting so profusely, so continuously that they need immediate relief for their health?

A I'm not sure.

Q You're not sure?

A I'm not sure I've ever come across a patient vomiting so much that they needed relief of the vomiting. They may need intravenous fluids rapidly, but relief of the vomiting is secondary.

Q We'll turn—come back to that. You agree that Phenergan IV is effective in controlling nausea?

A Yes.

Q And you agree or are you aware that there are emergency care textbooks—that's your field, right, emergency medicine?

A Yes.

Q That there are emergency care textbooks that recommend the use of Phenergan in situations

* * *

[249] help myself.

THE COURT: We'll continue.

Q Oncology, it's used in cancer patients quite frequently, isn't it, for nausea?

A It can be. I'm not sure how frequent.

Q Okay. The labeling indicates it can be used in amelioration of allergic reactions to blood or plasma. Are you aware of that use?

A Yes, but I don't—I've never used it for that.

Q Okay. How about for anaphylaxis as an adjunct to epinepherine and other standard measures be used in that situation, right?

A Well, that's—think—that's not a good use given that it even says in the package insert that the use of epinepherine with this drug is a problem. So this contradicts itself within the same package insert.

Q Okay, the only point I'm trying to make is there are several uses of this drug. It's not just nausea, correct?

A In the year 2000 there's—I think probably the only use of this medication would be nausea.

Q All right. So you think the FDA got it [250] wrong here, too, in approving a labeling that it has nine separate indications?

A I think that this drug is so old that many of these indications date back many, many years, and we no longer do these things. We no longer use this drug—given that many other drugs have come along—this is no longer a preferred drug for any of these indications. Not that it was never safe or useful.

Q Okay. I think we're in agreement. Of these nine indications how many of them does the package insert state should be given intravenously?

A Well, it says during surgery—special surgical situations it mentions intravenous use.

Q And I think actually in fairness, although it's not in the Indication section, I think you're flipping back later on in the Dosage and Administration section. There is a statement also I think about post-surgical—for post-surgical nausea and vomiting?

A Yes. It says for nausea and vomiting it may be given intra-muscular or intravenously and then pre-op and post-op.

Q Pre-op and post-op?

A It doesn't specify.

[251] Q Okay. Those operative situations would be situations generally when a hanging IV bag would be either set up or quite readily available, would you agree with that?

A I'm sorry, which situation?

Q Pre-op, post-op.

A There's probably one post-op. Pre-op there may be just what's called a saline lock.

Q Other medications that could have been used the day Ms. Levine came to the clinic, we talked about compazine. That has risks associated with it, doesn't it?

A Well, compazine has some of the same risks as Phenergan. It has no more risk and it has no risk of intra-arterial injury. So in other words, it has less risk than Phenergan.

Q Right, but it does have risks. You agree all medications have risks, correct?

A Yes.

Q I think you even testified that placebos have risks?

A Right.

Q So compazine has risk, right?

A Yes.

Q And actually Ms. Levine, I think Mr.

* * *

[267] said she was feeling pain or yelled that she was in pain?

A I know there was enough injected to caustic pain. I don't know the quantity.

Q It could have been one or two drops, right?

A And one or two drops have been reported to this caustic this problem.

Q There was an article in the literature that said there were one or two drops that caused the problem?

A There was what was described as two minims, which is an old-fashioned Latin term for drops, of diluted five cc solution, so it was even diluted and somebody lost a finger.

Q Okay. Dr. Matthew said that he was only able to find one case report in which 10 milligrams out of 25 had been injected.

MR. RUBIN: Objection.

Q Are you aware of that case report?

THE COURT: Hang on just a second.

MR. RUBIN: It's inappropriate for him to characterize. You can ask him in the form of a hypothetical, but for him to just say what someone—some other witness said and then ask him to

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[270] A No.

Q Okay. The labeling, the Warning section also instructs physicians to stop an injection if the patient complains about pain, correct?

A It does.

Q Okay, and that's an instruction to physicians and others who are administering this medication, correct? Stop.

A Yes.

Q Now, you gave some testimony about the phrase in the label that the physician should use an infusion—IV infusion set that is functioning satisfactorily, correct?

A Yes.

Q That can include a hanging IV bag. Correct?

A That could include that, yes.

Q And you've testified that it could include a butterfly set, correct?

A Yes.

Q Do you know how many times Phenergan has been given IV injection in the United States since it's been on the market?

A No.

Q Do you know how many times it's been

* * *

[272] THE COURT: I'll allow it for cross-examination.

A I believe that Ms. Fisch used the typical extreme care that clinicians use when they inject medications directly.

Q Okay. I want you to just assume for the purposes of my question that there will be testimony that Ms. Levine, when the injection began, yelled or screamed in pain. Was it extreme caution not to stop the injection at that point?

A If in fact Ms. Levine had screamed in pain, it would have been desirable to stop the infusion to see what was happening.

Q Okay. You mentioned the product Vistral. Vistral is a different drug than Phenergan, correct?

A Yes.

Q Different chemical makeup?

A Yes.

Q Different mechanism of action?

A Probably not.

Q Well, it doesn't have the nine indications that Phenergan has, does it?

A But it's an antihistamine, antinausea medication.

* * *

MARCH 9, 2004

* * *

[Testimony of Daniel J. O'Brien]

[10] care provider.

In the case of perhaps a serious adverse event being discovered about their drug, the manufacturer will write to say their obstetrician's using this drug. And there's something that the drug company—serious side effect or something that's been uncovered that they

will send out what's called a "Dear Doctor" letter or "Dear Pharmacist" letter and giving this updated information.

Q Now, does the drug company have the right or the ability to change a label without FDA approval?

A Under certain circumstances they can change the label without prior approval of the FDA.

Q Right.

A Usually if you want to change a label, which is—I'm talking about the physician's package insert now, for a new indication, say you want to treat another disease with it, you can't just do that. You have to submit data to the FDA for a new indication and get their prior approval. However, if there's a—you come across a serious side effect from your drug, you can change your label. There's a provision in the FDA regulations

* * *

[14] something about—that perhaps an instruction of how to administer a drug was not clear or not detailed enough or maybe a wrong—I hate to use the word wrong—but a better method might be used to administer the drug. So the manufacturer can just—can go ahead and instruct changes insert and publish that insert and distribute that insert with his strengthened or additional statements about—or instructions about the dosage or administration.

Q So if the company decided that it was unsafe to use a butterfly to administer a drug, they could change that without permission?

A Yes.

Q Advance permission?

A If that's what they felt, yes.

Q Number four, they can actually—it says, "To delete unsupported indications for use." Do you see that?

A Yes.

Q Would that include if it wasn't supported to use this drug intraveneously they could just pull this out?

A Yes.

Q Thank you. I don't have a slide for

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[18] some was provided to me. Well, the regulations, of course I looked at those. Adverse Event Reports.

Q And what was—what—what was the question about the product?

A Well, is there any reason to believe that the labeling of this drug was deficient in some way? Any way?

Q Okay. And what product were you looking at?

A Phenergan.

Q A Tubex injection product?

A It's an injectable product.

Q Do you know generally the method that was used to administer the product to Diana Levine?

A As I understand, a butterfly was used and a regular push syringe.

Q As opposed to a free-flowing IV?

A Correct.

Q Are you generally familiar with the difference between those two techniques?

A Generally, yes.

Q Was the technique used by Jessica Fisch, which the jury has seen, consistent with the instructions that were in the product information?

A It would be reasonably included, yes.

[19] Q Why is that?

A It was functioning properly.

Q So was an IV push system consistent with a system here?

A Yes. With what was used, yeah.

Q What is your understanding of what happened in this case? What happened?

A Well, I understand that she suffered tissue damage and resulting gangrene and which required an amputation.

Q And what was the product that caused that? Was it Phenergan?

A Phenergan, yes.

Q What about any other cause product, Demerol?

A No, not that I know of.

Q There was some indication that there may have been pain when this drug was administered; are you aware of that?

A I've heard that, yes.

Q And what is the relationship as a pharmacologist between the administration of this drug and the pain?

MR. HOFFMAN: Your Honor, I have an objection. If this is a nondesignated opinion,

* * *

[21] MR. RUBIN: He's not going to say that it was too late; he's going to testify that the causticity of the drug is consistent with pain. The pain is—

THE COURT: All right. That's not in dispute anyway.

MR. HOFFMAN: If that's all he's going to say, then I have no objection. I thought this was leading up to—

THE COURT: Fair enough.

(Open Court)

THE COURT: So I'll overrule the objection.

MR. HOFFMAN: I'll withdraw it on the basis of what Richard said.

THE COURT: Fair enough. That's fine.

Q (By Mr. Rubin) When there is pain when this drug hits tissue, what's actually happening?

A Well, there's irritation first and then if it's strong enough of an effect, you have cell death, actual cell death.

Q Is that what's causing the pain?

A The—first of all, the irritation would affect the nerve endings and right away cause pain. If it's severe enough, there would be—[22] cell death would occur. Just like we burn ourselves with a match or something, there are degrees of being burned.

Q Can you comment generally on the causicity or corrosive nature of this drug and the liquid that it comes in?

A Well, it's formulated to a pH, that is acidity or basis towards the acid side, and it contains phenol, which it can be a serious chemical irritant to the skin or even corrosive to the skin. There are numerous instances where the corrosive nature of this drug—by the drug, I mean the whole injectablbe formulation—causes cell death if—for instance, they say—the manufacturer states "Do not administer subcutaneously."

Q What's subcutaneously?

A Under the skin.

Q I need to take just a second and distinguish that between intra-arterially and intravenously.

A Well, that would be administered just under the skin.

Q Are some drugs—

A Not attempting to go into a vein or anything like that.

* * *

[24] A Yes.

Q And that's caused by—you believe—the corrosive nature of the drug?

A I believe so.

Q Do you believe it's a foreseeable risk that some significant danger or harm would happen if this drug is used with an IV butterfly push system?

A Well, certainly seems entirely possible—

Q Why is that?

A The manufacturer has stated not to administer this in a dosage more than 25 milligrams—dosage strength of more than 25 milligrams. They state that

their 50 milligram dosage form is not to be administered IV, strictly intramuscular use. They say to administer it very slowly over a minute or two minutes. This is an attempt to dilute what's going into the vein, go in slowly. It's like leaking, dripping something into a stream. You want to have it diluted, so that's an attempt to dilute it. The best dilution of all, although we have no real specific instructions from the manufacturer on how much dilution can put to the drug, it can administered—

* * *

[26] started to talk about the 50 milligram dosage is for intramuscular use, 25 apparently is for both ways. Go ahead with your answer about why this is not safe.

A Well, it's already happened administering the 25 milligram dosage form. When extravasated into the surrounding tissue it has caused damage, cell damage.

Q So therefore you wouldn't want to do that either way?

A No.

Q Are there any particular problems that can arise using the butterfly needle as opposed to a free-flowing IV?

A Well, you have the lack of a very large dilution for one thing. The needle could move and it could go through the vein or it could actually go into an artery and then you don't have the warning of feeling or having the back pressure from the—if you hit—go into an artery, you don't have enough force to push the plunger back.

Q Which means what?

A Which would mean help guide whether it's in an artery or not.

Q Was there anything in the literature

* * *

[28] Q What is Vistral?

A Hydroxazine and it had antihistaminic properties like promethazine for Phenergan.

Q What was it used for?

A The same sorts of thing Phenergan was used for.

Q Nausea?

A Nausea, hm-hmm.

Q And is that used for intravenous use anymore?

A No, it's been withdrawn. The manufacturer withdrew it.

Q It's still available though for intramuscular use, do you know?

A That I can't say for sure.

Q Is there any indication that this event was preventable? Well, let me ask a different question. Would you have an opinion as to the adequacy of the instructions and warnings contained in the product insert?

A Well, I—I thought it should state a free-flowing IV rather than just a functioning IV, which would allow use of the butterfly then—and I didn't think the butterfly should be used.

Q What about using it IV at all?

* * *

[35] A It used to be, yes.

Q Okay. And you even found out through your search that there were particularly abberant arteries in the arm, correct?

A In the antecubital fossa, yes.

Q Do you agree that the FDA knew about the risks associated with this product that we've been talking about? Yes?

A We certainly assume that, yes.

Q Well, you know?

A And they have discussed that.

Q This they have discussed that?

A In correspondence back and forth.

Q You've seen correspondence in which this risk that we're talking about has been discussed?

A Hm-hmm.

Q And you agreed that FDA receives adverse event reports from doctors as well as from the company, correct?

A Primarily from the company.

Q And the adverse event reports that we've been talking about that were in Wyeth's files you know were sent to the FDA?

A Yes, I asume that. I feel that, yes.

Q Did you review the New Drug Application?

* * *

[45] That's fine. Last time you published a scientific article was when you were a graduate school, correct?

A That's correct.

Q And you've agreed—you agree with me that one thing you haven't done over your career is offered your services as expert in any field of medicine?

A Oh no.

Q Oh no, you haven't done that?

A If it's—if it's—depends on how you use the term medicine.

Q All right. I don't want to debate with you about the meaning of the term medicine either. For your testimony at a deposition or trial you're paid $2,000 a day?

A That's my fee, yes.

Q You agree with me that the FDA has determined that the use of Phenergan is safe and effective consistent with the labeling that we've been talking about today, correct?

A The—it's still approved by the FDA, yes.

Q Well, in your files there is a letter from September of 1998 from the FDA to the company [46] saying the labeling that we're talking about here today is approved. Use it. Correct?

A Well, it says it's approved.

Q Okay. And we can agree that you disagree with FDA's conclusions?

A Yes.

Q Can we agree that since that letter in 1998 FDA has again on several instances reaffirmed that it is appropriate to market Phenergan with the labeling that we have here today?

A I don't follow what you mean by—

Q That there have been other approvals of the labeling of Phenergan that's at issue here since 1998. Or let me—maybe what's confusing is by my use of the word Phenergan. You understand that Phenergan as a generic product, correct?

A It is now I believe. Promethazine.

Q Right. And that there were other companies in this country who market promethazine as well as Wyeth who used to manufacture it?

A I understand that now.

Q And there have been companies who have sought approval from the FDA to market it using this label since 1998?

A I don't know the specifics.

* * *

[48] Q You didn't put into that search engine promethazine to see what's available from the FDA today on this product?

A No, I didn't.

Q Now, I think you testified—well, you've testified that you don't believe the benefits outweigh the risks for—

A No, the benefits do not outweigh the risks, yes.

Q But you agree Phenergan has some benefits?

A Yes.

Q Okay. And you actually found in your file a couple of secondary sources that you pulled out and copied and marked that say promethazine is an effective drug?

A Oh, I'm not arguing that.

Q That's great. Okay. We're making a lot of progress. You've offered the opinion that the labeling was inadequate?

A Yes.

Q But you will agree that the risk of inadvertant intra-arterial injection was quite thoroughly discussed in a package insert for Phenergan, correct?

[49] A The risk—yeah. I think so.

Q Okay. And you believe that a physician should read every section of the labeling, correct?

A I believe so.

Q And I'm sure probably everybody here agrees with that. And I think when Mr. Rubin was talking with you, he laid out with you a hierarchy of provisions in a labeling and I think that that comes from you. I've seen that in other testimony you've given?

A Yes.

Q At the top of that pyramid the most important thing is a contraindication, correct?

A That's the Thou Shalt Not part.

Q Right. And you agree with me at the very top of the pyramid there is a Thou Shalt Not about intra-arterial injection of this product, correct?

A Oh, yes.

Q And at the top of this pyramid there is also a statement that says "Preferred route is intramuscular, not IV." But it doesn't prohibit IV use. We're not contending that. Do you agree with that?

A Yes.

[50] Q I can give you the package insert if it—we've talked about the contraindication section the Thou Shalt Not?

A Yes.

Q The next section you said in your pyramid, your hierarchy, are warnings?

A That's correct.

Q There is a section here in the warnings, its own section about inadvertant intra-arterial injection, correct?

A You're in the warning section, is that correct?

Q Yes, I am. There is a bolded top of the section, bottom of the first column of the label?

A Oh, okay. Yes.

Q Okay? And it discusses the risk of intra-arterial injection at length, doesn't it?

A Yes.

Q It talks about the close proximity of arteries and veins? In places where intravenous injections are commonly given?

A Yes.

Q It says that extreme care should be exercised to avid perivascular extravation or inadvertant injection, correct?

[51] A Right.

Q You understand that what happened here is that there was an injection into the artery, correct?

MR. RUBIN: Objection.

MR. HOFFMAN: This goes back to the stipulation yesterday, your Honor. I mean I—

MR. RUBIN: He can say what he understands.

THE COURT: I didn't—I think this is the wrong witness for this question. All right? He wasn't there. He doesn't know so I'll sustain the objection and ask you to continue.

MR. HOFFMAN: Okay.

Q You were asked some questions on direct about your understanding of what happened on April 7th, 2000, correct?

A Yes.

Q And the judge just pointed out you weren't there.

A Yes.

Q But you did read some depositions, right?

A Yes.

Q You read Diana Levine's deposition, the

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[Testimony of Jessica Fisch]

[62] goes by that I don't think about this horrible accident. And no matter how awful I felt during this period of time, I've always felt completely self-indulgent because I know the amount of pain and misery that this woman has been forced to bear because of this accident. There's not a day that goes by that I don't feel a great sense of grief over it. It's probably the worst thing that ever happened to me in my life.

Q Do you feel like you have any responsibility for what happened?

A I feel like I was the hand of God. I feel that—I feel that a tragedy happened when I was trying to help somebody when they had come to me for help; when they trusted me to give them help; when I trusted my own abilities to try to alleviate her pain that day. And I—I hope nobody ever—I hope none of you ever has to be in the situation. It's been almost a living hell.

Q You saw Diana on April 7th. I'm going to go back to what happened. You wanted to tell Diana that, what you just said?

A How badly I feel?

Q Hm-hmm.

A I don't have the words, but I want you [63] to know that every day for many days it's the first thing I think about. For a year there was a time when I wouldn't be able to use my right hand to do things. I couldn't—I couldn't focus. I couldn't sleep. I kept thinking about what had happened and how much pain she's been in and how much suffering happened because of this. I would have gladly cut off my arm. I would have given her my arm. I would have killed myself if I could have at times.

Q What was her condition on April 7th?

A She—she had come to the clinic in the morning. Diana had severe migraines. Migraines that were almost intractable in nature. She would not only be in terrible pain, she would not be able to sleep, she would be vomiting, she couldn't bear light or sound, and they happened fairly regularly for her. She really had been a good patient. She had been trying every possible way to do medications to prevent her from getting headaches.

Q When you saw her on April 7th what was her condition?

A Well, she had been seen in the morning and was treated for her migraine headache earlier that day and she had been brought back to the

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[65] Demerol.

Q Why—what's the Demerol do?

A Well, Demerol is a narcotic. It's used for migraine headaches or severe pain. Migraines that Diana had in the past had been treated with Demerol and it had worked well.

Q Why did you decide to give it to her intravenously?

A Well, she had had an injection of intramuscular Demerol and Phenergan in the morning and it hadn't worked at all. So I felt that in order to give her some relief, that I would give it intravenously and try to get it in a more effective and swifter manner.

Q Have you given—are you authorized to prescribe and administer narcotic pain medication?

A Yes.

Q And how frequently have you done that over the years or weeks?

A I—probably given upwards of 75 IV injections of Demerol and Phenergan in the last ten years.

Q So you also decided to give her some intravenous Phenergan?

A Well, yes. I mean I was starting an IV, [66] and since I was going to be giving her the Demerol IV, it

didn't make any sense not to give her the Phenergan in the same route.

Q What's the Phenergan do?

A Well, Phenergan is a drug that's used for a number of things. It's basically used in practice for, you know, nausea and vomiting.

Q So—

A Sometimes.

Q Why do you give it—I know Dr. Matthew testified to this, but why do you give them together?

A Well, sometimes Demerol can make people more nauseated when they get it. Certainly that day Diana—she was getting dehydrated. She had been vomiting so much she couldn't keep anything down so she certainly needed something for vomiting. The other thing is she hadn't been able to sleep because of the pain and often Phenergan, which is an antihistamine, it can cause some sedation and it can help people sleep.

Q Is a prescription for Demerol and Phenergan common for the treatment of severe migraines?

A It was the standard of care in our [67] clinic. It's the standard of care in many hospitals, and many other sites.

Q Now, you decided to give her 50 milligrams. Why 50 as opposed to 25 or 75?

A In the morning she had gotten 25 milligrams of Phenergan and it hadn't worked so I increased the dose. And since it was in keeping with what was in the product information, I didn't have any second thoughts about giving her 50.

Q And how did you get the medication? Who set it up for you?

A I asked our nurse Pam Woodworth to go get the medicine. She went and got an IV set and the medicine I was going to need.

Q And why did you decide what method—we'll talk about the specifics in a minute—but what method of IV administration did you use? The free-flowing or the push method?

A I gave it to her by IV push through an infusion set which was in keeping with what the instructions were for the Phenergan.

Q Why did you make that decision as opposed to setting up a free-flowing IV?

A Well, you know, at the time I was anticipating just trying to get away to get the [68] medication into her in a swift and timely way. We usually set up a hanging IV like if somebody's had a heart attack and you're going to start an IV because the person's going to need ongoing treatment through that IV placement. But for Diana it was just a matter of, you know, five minutes worth of medication administration so I didn't go to the trouble of hanging an entire IV set.

Q What did the LPN bring you?

A Pam brought me—she brought me a tourniquet, she brought me alcohol prep pads, she brought me gauze, she brought me a syringe, a 3 cc syringe that had 2 cc's of Phenergan in it. She brought—

Q One second. I think that's it. Right. Why don't you open that up.

A So this is a tourniquet which probably most of you are familiar with and alcohol pads.

Q Keep your voice up.

A Alcohol pads. And this is a butterfly infusion set which is customarily used. And the medication came in syringes like this with the needle. And usually what happens is the nurse will take the needle off before giving it to me. So there was 2 cc's of Phenergan in one of these. And **[69]** then another 3 cc syringe there was the Demerol.

Q Let me just ask this. You got a syringe with the Phenergan in it?

A Yes.

Q How much fluid did that syringe—would it have held if it were full?

A Up to where this barrel is.

Q If it were full it would be 3 cc?

A If it was full, it would be 3 cc's.

Q And how full was it?

A It was this full, 2 cc's.

Q Okay. So what is the significance if you're administering Phenergan? What is the significance of there being 2 cc's of liquid in that syringe she gave you?

A Well, the Phenergan that we had at the time came in what's called the Tubex.

Q There is an example of a Tubex here. The jury has seen it, but I'll show it to you.

A Tubexes come like in a cartridge like this and they're filled with a certain amount of medication. And they lock into a device that has a plunger on it so that you can give the person an injection.

Q Why didn't you use the Tubex with the [70] needle on it and just plunge that into her vein?

A Well, one of the—

Q As opposed to having it transferred into a larger syringe?

A Well, one of the things that's nice about using a butterfly is that you can place it in the vein and then you can stand back a little bit from the patient. And even if they move a little bit, it's not going to affect the injection, like if you have a needle directly into a vein, if you're mainlining something. The fact that it has tubing also lets me see that blood is coming back into the tube normally from a proper placement.

Q When the blood comes back into the tube after you've placed the butterfly, what does that tell you?

A It tells me that things are where they should be in the vein because in pulling back on the syringe, which is—can I show—

Q Yeah.

A Okay. So what we do is have this in a vein and then we pull back—

Q Let me hold it for you. The eggplant disappeared here.

A What we do is pull back and blood will

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[73] well.

Q So why did you decide to use this butterfly infusion set as opposed to a—was the free-flowing IV method—would that have been safer?

A I believe it would have been safer.

Q Why?

A Well, God, there's a couple of reasons. You know, if you have a hanging bag of saline, you've got more volume of liquid that's going into the vein probably at a fairly good flow. If—if the catheter were placed so that there was inadvertent injection into an artery, you know, there would be back pressure on the catheter so that it wouldn't flow in. You know, also I don't know if anybody has ever seen an infiltrating IV siting, but it forms a bolus, a bubble, under the skin if something isn't placed correctly. And with a large volume of saline in a hanging IV, that would be easier to see than if it was just a tiny amount of volume from the Phenergan itself.

Q So if you let the—

A IV run.

Q —before you put in the medication?

A Right. You would see if it was [74] infiltrating. And if you were in an artery, it would cause back pressure and wouldn't run correctly.

Q So why don't you use the free-flowing IV? I think you've answered that because you wanted to—it was just a single dose?

A Right. It was just a single dose. I just wanted to get the medication in in a quick and effective manner.

Q So can you explain why the use of the butterfly infusion set is okay and consistent with the instructions?

A Well, it is consistent with the instructions. It says so in the product information, if you read all the way down, that it can be administered through, you

know, what they call a rigid needle. It says that you have to be careful, and I am careful, and I was careful that day. So I feel that it was consistent with how the product described it should be administered.

Q People have talked about aberrant arteries. What knowledge or awareness did you have of a possibility of a misplaced or abberant artery at the time you were doing this injection?

A It never crossed my mind.

[75] Q Why not?

A You know, there was no mention of it in the product information. I had never thought that—I was using a very small needle and I was in a very shallow vein, I just didn't know that there could be an aberrant artery.

Q Well, didn't you take anatomy in your courses?

A Yes.

Q Wasn't there a mention of aberrant arteries along the way?

A No. There's only about a three percent aberrant artery occurrence; just wasn't something that I was aware of at the time.

Q There has been conversation here about whether Diana complained of pain. What is your recollection?

A I remember she said it was—she said "It burns," and, you know, I glanced up and I—and I looked at how the medication was going into her arm. And everything seemed the way it had always seemed and I'm used to people saying that medication hurts when I inject it. It's something that happens probably

every time I've given a shot so I told her "It will be over soon."

[76] Q How long did it take you to inject this medication? Phenergan?

A Probably about three to four minutes.

Q And did she complain of pain throughout the entire process or just at the beginning?

A No. She didn't complain through the entire procedure.

Q Why didn't you stop?

A Well, I—I—I looked—I looked at the IV site and it looked fine. It looked like the Phenergan was flowing in normally. And again, you know, it wasn't like she sat bolt upright and ripped something out of her arm. She said it burned and I just thought it was—I mean it's just crazy to have that phrase be the reason why you should be worrying about an IA injection. I mean it just—it's all over the place. I mean how can I make a judgment call on somebody who's writhing in pain with a headache and saying that the medicine burns? Does it burn like a lightning bolt going through your—I mean it's just so interpretive. I mean everybody complains of pain usually when they're given an injection. It's just a vague instruction. I—certainly it would get my attention now knowing what I know, but at the [77] time it just didn't seem like she was screaming in pain.

Q After you completed treating her did she leave?

A Yes.

Q And she came back?

A She was brought back, yes.

Q About four o'clock?

A Yeah, she called and said that her arm was cold and I told her to come right up.

Q Were you there?

A Yes.

Q And did John Matthew come in?

A Yes.

Q And what involvement did you have in her treatment after she came back at four o'clock on April 7th?

A Well, you know, we examined her and her arm was blue and cold and she was very uncomfortable.

Q About the headache or the arm?

A About her arm.

Q How was her headache?

A I really don't remember.

Q Go ahead.

* * *

[81] excuse for taking somebody's arm and having some kind of an extravasation injury that means that they lose their fingers or their arm. It's nausea. It's not—this isn't—this isn't a heart attack, this is somebody who's sick to their stomach.

Q Does Wyeth send representatives to the Health Center?

A I see a Wyeth representative once or twice a month.

Q And what goes on? What's the relationship between the clinicians like yourself and the—what do they do, these representatives who come by?

A Well, their job is to get you to prescribe their medicines because that's how the company makes money. Supposedly it's to keep us abreast of information and to let us know about any problems that the medications might have had. The person—

Q Who—go ahead.

A The person who was the rep for Wyeth Pharmaceuticals—we've got at least three pharmaceutical reps from Wyeth that come every month right now—but at the time that this

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[86] just setting it up. That doesn't include starting the IV.

Q Okay. But there was a 20 minute period—

A I went to see other patients, scheduled patients.

Q You went on to see scheduled patients?

A Yes.

Q You testified earlier that you used the butterfly because of the convenience sake for Diana, as I understand it, that she was just going to be there, get the shot and go along back to her home?

A Yes.

Q And does the butterfly—could you take out the butterfly if you would please.

A I think I might have been playing with this.

MR. RUBIN: I don't think you need to take the needle off.

MR. O'ROURKE: No, I just want the butterfly. That's why it's called a butterfly because of the two little wings here?

A Yeah.

Q Now, do you normally tie those down with [87] a tape or with adhesive when you put them for an antecubital injection?

A Sometimes.

Q Why do you do that? Why do you tie them down with a tape?

A Well, if you're putting it into a very superficial vein and there's a lot of potential movement you might tape it down so that the position of the butterfly isn't jostled.

Q And is that good medical procedure to do that?

A I don't think I could use an expression like good medical procedure.

Q Well—

A It's—

Q Let me ask you what the standard of care is, that you should tape it down?

A I dont know that that's the standard of care.

Q But in any event in Diana's case you didn't do that?

A I did not.

Q Do you have some judgment as to what percentage of the cases that you have used this butterfly

that you would have taped it down in the [88] patient where you were going to give the injection into the antecubital area?

A I would say that the only time I've taped down the wings on an infusion set was when this was attached to a hanging IV bag which usually in our practice was to administer an IV antibiotic over about 20 minutes. The rest of the time neither myself nor any of the other practitioners in my clinic routinely tape down the wings of butterflies when it was used just for a very short infusion.

Q Would you use the butterfly that—if you were using a hanging bag or would you use a different type of infusion?

A Sometimes we will use butterflies, and sometimes we use intracaths.

Q You didn't actually mix the medication, did you, or prepare the medication I guess—

A No.

Q You said Pam Woodworth did?

A Yes.

Q Now, have you had an opportunity since the time that this incident happened to talk with Pam Woodworth about this?

A We've discussed it. We—I'm not sure

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[90] A I read that, yes.

Q And did you read that she also said—referring to page 123 at line 16—"it was one of the most extreme pains I've ever felt"?

A I read that.

Q All right. And did you read that she said that you said that "you just got to stay there and be quiet so you don't dislodge the needle"?

A I don't remember that part.

Q And—but in any event, did it ever cross your mind at any time to stop injecting the medication?

A I briefly thought about it. I, you know, I looked down at the IV site and nothing seemed amiss. And although Diana, you know, in that statement she said she was screaming, I don't remember that she was screaming. I remember she was speaking in a normal tone of voice and said "It burns."

Q And did it take you two minutes to inject the Phenergan?

A Probably a little bit more than two minutes.

Q And can you give us some judgment then as to how long it took you to inject the Phenergan?

[91] A About three minutes.

Q And you were aware at that time that the literature, the labeling of the drug, says that if a patient complains of pain you should stop the injection?

A Yes.

MR. O'ROURKE: That's all I have. Thank you.

THE COURT: Anything further, Mr. Rubin?

MR. RUBIN: No. Thank you.

THE COURT: Ms. Fisch, thanks very much.

MR. KIDNEY: Can I have a minute, your Honor?

THE COURT: Absolutely.

MR. KIDNEY: Your Honor, our next witness will be about two or three minutes.

THE COURT: Okay, everybody stretch for a minute.

MR. KIDNEY: Thank you. Call John Gailmore to the stand.

JOHN GAILMORE, duly sworn

Direct Examination by Mr. Kidney

Q Good morning.

A Hi.

Q Could you state your name please?

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[Testimony of John Gailmore]

[93] the purpose was to—to celebrate children and childishness and the creativity that is inherent in kids and to encourage them to never forget it and keep it up.

Q John, do you know Diana Levine?

A Very well.

Q How do you know her?

A Well, we've known each other almost since I moved to Vermont in 1977. I went to see her sing and I heard her on WDEV often, both as a solo artist and with her sister Liz.

Q Liz is sitting right here?

A They had a magnificent duo called the Winn Sisters, oddly enough, and they wrote songs and sang and it was a totally unique and joyous sound.

Q Did you ever play on the same bill with the Winn Sisters?

A Quite a bit, yeah.

Q So you've seen Diana perform?

A I have.

Q How was she as a performer?

A Well, she exuded warmth and joy and I very much related to her style and her attitude because she too found—had discovered why she's **[94]** here and what she's on earth to do. And so have I. And there's nothing better than that sensation to have—to have discovered what you're here for and to be able to pursue it is just beyond description.

Q John, you've seen a video clip of Diana performing, is that correct?

A I have, yeah.

Q And I think she's playing "Mr. Postman"?

A Correct.

Q Do you think that that video clip is a good example of Diana Levine as a performer?

A Oh, it's an excellent one. You can see—you can just see in her body language and in her facial expressions and the whole—just the whole performance, you can see the joy in her. And you know when someone is doing something that is a natural thing for them to do and is their passion, you can see it. It's very evident.

Q John, I want to show you Exhibit—Plaintiffs Exhibit 32. Is that in fact the video clip that you were shown?

A It is.

MR. KIDNEY: Your Honor, I move to introduce Plaintiffs 32 and to show it to the [95] jury.

MR. O'ROURKE: No objection.

THE COURT: Okay. Thirty-two is admitted.

(Plaintiff's 32 shown to the jury.)

Q John, could you just comment on that clip in terms of Diana as a performer—I guess that was at the City Center in Montpelier concert?

A Yeah, I'd love to comment on it. I see myself in her because it's hard to describe the feeling of—of doing the natural thing and doing what you're supposed to do in life and of just affecting people and making music and just—I'm not a religious man, but you know, of carrying forth and of pursuing what you're here to do. And you can see it in her and I was looking at her hands, too, as I watched the video, and I was particularly looking at her right hand, which is the really important hand in terms of—of carrying through from the heart. It's the one that—that controls the rhythm and the whole feel of the song. The left hand is playing chords, the right hand is the joyous hand. That's the one that's—that's doing the picking or the finger picking and is the real controlling hand in terms [96] of the feel of the song. And it was beautiful to watch.

Q Well, speaking of hands, could you talk about the creative process and how, if at all, hands are involved in that?

A Well, everyone creates differently. I have written songs where I've just written a poem and then put to music. I've also written songs where I have just been in my studio fiddling around with the guitar. And the chords, the progression of chords and the rhythm conjurs up a subject; just the beauty of the chords and

the rhythm conjurs up the subject. So oftentimes I will create through my hands. I will—I will—just my hands will be creating independent of anything else. They'll just be creating and that will make me think of a subject and will cause true emotions in me and that will make a song.

Q Well, for someone who is a singer/songwriter like Diana, then what does the loss of a hand mean?

A It means that you—you lose an integral part of your creative process. And your—you lose an essential part of your act to express what you feel in your heart and there is no [97] greater loss than that. It's a paralyzing—emotionally paralyzing thing to lose. And I will reiterate especially the right hand in a guitar player or in a bass player, which Diana does both, because if you've ever seen—well, you saw her hand playing bass, really you can do wonderous things with that right hand and losing that all you can do is play chords and imagine the rest. So it's a terrific loss.

Q Now, were you familiar with the Re-bops?

A Yes.

Q What can you tell us about them?

A Well, you know, to a great extent, the Re-bops do exactly what I try to do with kids is to make them feel like stars, and to just boost their self-image and to give them the opportunity to flourish and to be creative and to sing and to do what kids do naturally, which is to sing songs and perform. And kids are hams by nature. And so the Re-bops gives them a chance to do all those natural childish things.

Q So in your opinion, John—well, strike that. I'll just ask it this way. How important over the 27 years that you've known Diana was her music to her?

[98] A Well, I'm not sure there are words to describe that. It meant everything to her. You could see it in her performance. You could—we talked often about how lucky we were to be doing music for a living, how lucky to have found our passion and to pursue it, to be able to pursue it. And it's a loss of a fundamental part of your being. She still had a lot of love around her from her friends and her family, but to lose the ability to make music and to express her heart is irreplaceable.

Q In terms of expression, I mean as a non-musician, does a musician express both joy and sadness through their music?

A Oh, all of it. Yeah. And you can express—I mean the arts is the best vehicle for expressing emotions. Music more than any other I think because it's immediate and it goes right to the spine and you can express profound sadness and tragedy and the ultimate joy and everything in between. There's nothing that music can't express emotionally.

Q Well, would this be an example of the joy?

A Oh, absolutely. You can see it in her.

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[100] sadness and to make—to make beauty out of it. And also to express hopefulness at the same time.

Q So how is Diana going to get through this tragedy without her music?

A Well, Diana will because of her strength. Her life will never be the same. She'll never be able to make music the way she did. She'll always be able to make music because of the music in her, but it will never be the same without that hand. That is a—a fundamental basic loss that can't be replaced. She will get through it because of the love of all of her family and

friends around her and her music will still be beautiful, but the process will be different and it will—her music will never be as close to her heart as it was because of the loss of that conduit really which is what a hand is, an arm directly from the heart.

MR. KIDNEY: Thanks, John. All I have.

MR. O'ROURKE: We have no questions, your Honor.

THE COURT: Mr. Gailmore, thank you very much for coming.

MR. RUBIN: If the court wouldn't mind, we would like to break a little early.

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[Testimony of Jessamin Levine]

[105] the Re-Bop business, what was it?

A Well, my mom was just like really brilliant with kids. I mean she could bring them into any space and just draw—evoke these amazing things out of them, spontaneity, playfulness and the kids were really a huge part of the creation of the music. And it wasn't like she was a dictator. She was definitely a collaborator. And there was this—one of the albums is called "Raised on Rock and Roll" and it's like "Raised on rock and roll, raised on rock and roll. I was born to boggie, I was raised on rock and roll." And that was like—my mom and dad wrote that together and it was really pretty autobiographical to me. I was.

Q Raised on rock and roll?

A Yes.

Q So obviously the Re-Bops meant a lot to you. What did they mean to your mother? What did the Re-Bops mean to your mother?

A It was really her life. When she found this way—she was very lucky to find this way where she could incorporate her love of music and her love of children and there were these perfectly interlocking loves. And then without her ability to make music, like she used to—there's this **[106]** dangling love and I'm sure she'll find ways to work with it, but it's definitely not the same.

Q And your dad was in the business, too?

A Yes. He was the engineer.

Q So how about outside of the Re-Bop business, what was your mom like as a mom?

A She was just so active and artistic and giving is probably the number one word I would say is giving, giving, giving, always thinking of others, joyful. She did poetry and pottery and photography and athletic things like skiing and tennnis and swimming. Just very well rounded, very exuberant person.

Q I mean we all use our hands a lot obviously, but was your mom—how would you describe her in terms of her relationship with her hands and who she was?

A Well, I think about my birthday parties and every year there would be some theme that I would pick out and she would just go all out with them in the craziest ways. Like one year the theme was rock and roll and there was this cake that was probably as long as this stand, maybe even longer. It was turquoise with a lightning rod. It had like Reese's Pieces knobs and licorice strings and it

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[108] supposed to be the one calling me up at college and saying "Are you eating well enough?" But she knows I have everything prepared for me there. And whenever I call, I'm like "Are you eating well?" Because she really can't cook for herself in a way that's nutritional. And like I came home and all the heavy, cast iron skillets were gone, which were like the best skillets to cook with, but she was just using them because they were there and it was hurting her even more her remaining arm, the tendonitis she had. So she just got rid of them.

Q Has she baked at all since this tragedy?

A She has tried to. It still tastes good. It just takes a lot longer and anticipate the hunger. And she made Christmas cookies this year. Every year she makes really elaborate Christmas cookies to hang on the tree, and I could hear like noises of frustration coming from the kitchen, but so it's not like it was—it's a joyful process anymore. It's a lot more grudging. So she doesn't do it basically.

Q I think you talked about this a little bit. Could you just tell us about how big a part music is in your mom's life?

A It's just so huge. When she's soaring, [109] when she's joyful, that's how she expresses that. When she's down in the gutter, that's how she resonates with that and rises out of it. So it really was her therapy and it—I mean I've learned just the power of music to heal is so immense and I use it in my life. But I just remember ever since I was little, whenever my mom seemed sad or something, she would just go pick up her guitar and work through it with her music. And her album "Sink or Swim" after my dad died was like—that's what

she was working through, her grief, and I don't know how she would have done that without her music.

Q Do you play music?

A I do.

Q What do you play?

A I play mostly guitar. I'm trying to learn bass a little and a little drum set, a little hand drum and steel drum.

Q What's your mom play?

A Right now?

Q No, what did she play?

A Oh, she played bass and guitar and piano.

Q Are there many female bass players out [110] there?

A No. There should be.

Q So music was a big part of your family life?

A Yeah, and we used to play music together. Like on the songs I'd written she would make up bass lines and I would be like well, I don't like some of her rules, but if she makes bass lines like that, she has to have some authority, you know.

Q Did you—I asked you to show me some pictures that kind of show you and your family and the musical connection. Did you give me those? I'm showing you Plaintiff's Exhibit 37 and 38.

A Yes.

Q Okay. Was there also another picture which we've already talked to Mr. O'Rourke about—and we don't have a hard copy, your Honor, but we'd call it

Plaintiff's 39 and we'll get it in—we've got it on the screen, but we don't have the hard copy. We lost that.

MR. O'ROURKE: No objection to that.

THE COURT: Fine. So 37, 38, 39 are all admitted.

Q We're going to put these up on the [111] screen and you can just tell the jury about these pictures. And so we've got this picture. Can you tell the jury about this?

A That—

Q Wait, Mr. Rubin has to move for you I guess.

A That is me, my mom, and my dad and I was raised on rock and roll, and that's evidence of that. And that was before I started playing guitar, but I started pretty young, when I was like eight or nine.

Q All right. And why don't we go to the next picture. That's going to take a second.

A That is my mom on the bass and me on the drums. And I remember I think my band teacher at school—I had played bells, too, actually and he said oh, you'd be a really good drummer. And I was kind of like, well, I've never seen girl drummers before, even though I was all about girls, too, you just—my mom encouraged me so much to play the drums and—and we jammed together.

Q So did you make a lot of music with your mom over the years?

A Yeah.

Q Okay. And we'll look at the last

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[114] in. And I mean I'd seen her in pain over the loss of my dad, but this was like physical pain and she sounded like she was having a baby. It was really traumatic and her arm was swollen—so swollen. Every day it would get more and more swollen and blue and I was like—I would massage it and put water over it and try to take care of it, but I mean we just all could sense that something was really wrong then. The pain was so great and it was hard because I knew that no matter how much pain she was showing that she was in, she was in a lot more pain than that. She's always like—she's always tried to shelter me from pain.

Q How about fear? Do you remember any of that?

A Well, a lot of fear, just not knowing exactly what was going on and and having some sense of what it would mean to lose her arm, but never—never being able to predict how many different ways it would affect her.

Q And that was when your mom was at home after the shot of Phenergan?

A Yes.

Q How many weeks was that?

A I don't know. To be honest, like all [115] the details of that time, many are very blurry for me because I was just very emotional and kind of trying to be a little uninvolved so I didn't break down.

Q Did you ever see your mom up at the hospital up at Dartmouth? Or down at Dartmouth I should say.

A I went a few times. She really didn't want me up there again protecting me from how horrible it was, but one of the times I went I brought members from

Village Harmony and we serenaded her and she just loved it. She was crying and smiling and—

Q What about when your mom got home from the hospital? What was that like? After the amputation.

A That's when it really started sinking in because she would be trying to do all the things she ordinarily did and she just couldn't do them. At first she couldn't even lift her—like had very serious mobility problems as well and she was doing physical therapy for that, but I mean she couldn't tie her shoes so she had to go buy Velcro shoes. She couldn't open jars so I was opening jars for her. I felt like the principal like [116] helping the kindergarten kids at school or something. It was just very strange and surreal because the roles were really reversed a lot of times. And to have to be the mother of my mother was bizarre and I never—I just became so grateful for my arm and I missed her arm so much like her—both her arms being able to rub my shoulders or play music or—I mean it was amazing how many—how many times I was just like wow, what would I do if I only had one arm in that situation?

Q What kind of things couldn't she do?

A Well, she couldn't do—she had to totally reconceive of the way she did the most basic things like even getting up in the morning. She couldn't make her bed so she had to have someone help her with that just like putting the sheets on the bed. Buttoning up her shirt or getting her clothes on. Even today I was just struck by that again like trying to decide what to wear. All of the girls like getting together to try to look—I mean we were professional, but just how long it takes her to get dressed is amazing. And on top of that, I mean she always used to just whip through the mundane or the [117] everyday things, you know, and like cooking and

cleaning and now she can't really do any of the creative things because it just takes so much longer to do all of the basics.

Q So now it's almost four years later, right?

A Yes.

Q Tell us what you think your mom has lost as a result of this tragedy.

A I think she's lost a little bit of her mind. I mean a part of her is gone. It's like her best friend in a way, her arm, because that's what allowed her to make her music and to do all the things she loved, but also just to do the things she needed to do. She's not the same person. Like when you're sitting next to her, you can feel her grief and you can feel everything she's been through and she still tries to be strong and you can admire her for that, but she's a totally different person.

Q Does your mom ever get bitter or angry?

A No. And that's just been a very valuable lesson to me. She's so forgiving and—if she ever has had resentment, I have not seen it before she let it go, so I couldn't tell you.

[118] Q How does she deal with it? How does she cope?

A I think she—she just takes triumph in the little things that she is able to do. I mean it reminds me of like the Sesame Street episode that I had taped from when I was little where the little kids learn how to put on their clothes and they're so excited and she is so excited when—or when she finds new ways to—that makes things easier. Like she found this contraption that has a suction cup and a nail cutter, nail clipper attached, too, so now she can clip her nails. She just takes joy and she bounces back a lot, but it's because

like she's fallen. She has to trip over and over again. It's like oh, I can't do this the same way anymore. She's tried to rearrange the house so everything is easier. She leaves the doors a little bit open so there isn't so much friction because she has to be so careful to protect her remaining hand, but I don't honestly know how she does it. I don't know how I would do it.

Q So you think your mom will make it?

A I think she'll make it, but it's just going to be so hard and I mean she—I just think [119] of her as such a joyful person. And when I think of all the things that she used to take joy in, everything is so difficult now. And I don't know how she could keep on shining through that. But when she sees the most depressing movies she will be like "Oh, I thought it was uplifting," and we're all like "You're crazy," but it's because of endurance and she knows—she sees that reflected because she has had to endure so much and she sees—she gets a kick out of symbolism and stuff like that. So when she saw the movie "Finding Nemo" because he has like this little fin, he was born with one tiny fin, it's called his lucky fin, but he still goes on a huge adventure and swims through it and is strong. So she takes joy in stuff like that. But she stumbles so often and I don't think any of us can imagine what it's like for her. Especially losing her music. I mean that was her foundation, that was her rock that kept her sane and gave her the drive to keep going.

Q It also allowed her to soar?

A Yes, and to make connections with people. I mean a lot of her friends—most of her friends are musicians and that's what they would do together. So she's going to have to reinvent her [120] relationships and the way she moves through space, just the physical reality

of it, and invent a whole new conception of herself because so much of her self-image has been affected so much by this. And she still does go out and makes public appearances and is involved in the community, but it's so much harder for her because she's not symmetrical.

MR. KIDNEY: That's all I have, Jessamin. Thank you. Mr. O'Rourke might have a question or two for you.

MR. O'ROURKE: We have no questions. Thank you very much.

THE COURT: Thanks very much.

MR. KIDNEY: Call Steven McArthur to the stand.

STEPHEN MCARTHUR, duly sworn

Direct Examination by Mr. Kidney

Q Good afternoon.

A Hello.

Q Could you state your name?

A Stephen McArthur.

Q And where do you live?

A In Berlin.

Q Who do you live there with?

A With my wife Ricki.

* * *

[Testimony of Stephen McArthur]

[130] as well as a fellow musician and a former business colleague. Can you tell us what she was like before her amputation?

A Unstoppable. Overwhelming. Just on the go. Just an amazing energy. Both my wife and I talked about how we just couldn't keep up with her. We never knew where she was going next, what she was doing next, what project she was doing next. Musically she was doing a lot of other things. She was playing with other bands. She was playing with small groups, some large groups. I was invited at one point to—not long before the accident happened I was asked to play with her up at a big club in Burlington with a band she was playing with, which was a nice honor for me to be asked to come and play with her. But yeah, she was just full speed ahead with the record business.

Q How about outside of music? What kinds of things did Diana like to do?

A At one time she was a potter. Still a kiln I think on her porch. Her photography, her—some of her writing, her song writing, which is in and of itself poetry, was always something she—she did cooking. We'd go over and have these wonderful meals. Her kitchen is one of these [131] eat-in Vermont kitchens in an old Vermont house. Active. Lots of friends, people over at the house all the time. She was on the go all the time.

Q I want to talk about the year 2000. Did you see Diana up at CVH?

A Yes. We got a call saying that something had happened. We didn't know exactly what it was. I think her sister called, but we—we went up immediately, as soon as we heard she was there, and first thing we noticed was her arm and how it was wrapped up and you could just see the fingertips. They were dark I mean at the time we didn't know what was happening; the doctors didn't even know what was happening. Every-

body said oh, this is just going to get better, but as we all know, it didn't.

Q Did you see her up at Dartmouth? Or down at Dartmouth?

A Yeah, we saw her a few times at CVH, then we heard she was going to be transferred down there. The first time we went there, it was very clear that the doctors—this was not something that was going to recede. That what they were doing was trying to figure out how far it was going to go before they operated and took off whatever [132] they had to take off. At first when we talked to Diana the first time, it was well, maybe it would be just up to the fingertips, or the next time it was um, maybe the knuckles, and then oh, maybe just half the hand or maybe to the wrist. Well, it wasn't even the wrist, it just kept on going. So every time—every time we went just, you know, just—it just died a little more.

Q You were there. Tell us what the hand looked like over the course of this month at Dartmouth. Tell us what you saw.

A Black, bloated—I mean I don't even think—somebody used the word gangrene, but that's—you know, I've seen gangrene in the movies. To me that's what it looked like. It just looked like it was just rotting flesh. It was just awful. It was awful.

Q If you could just tell us what that whole experience was like waiting for those three weeks when she first got there, when they did the first amputation. Just tell us what happened up there, what it felt like, what you saw, what Diana went through.

A Yeah. I mean for us it was bad. But for Diana, we couldn't—we couldn't even get our [133] minds

around. She was sitting in this bed and dealing with this life altering experience surrounded by friends and family, a lot of pain, deathly afraid of any kind of needle because that's where it all started. They had to take blood tests, they had to give her medication, they had to use needles. And that needles in and of themselves became this—this—this like horror thing for her. So, you know, we would be there and they would come along, well, we have to take some blood and it was—she'd start shaking, crying. She was in pain. I mean for all of us being there it was one thing; for Diana in that bed it was something that none of us can—I mean I've thought about okay, well, if I lost my arm, I wouldn't be able to play sax again, but kind of big deal, that's like a hobby for me. I was thinking about her, something that was so integral to her existence, playing instruments. I just—I couldn't get my mind around that.

Q When you describe the hand, was it moving from the fingers up the arm or was it just black and as you described it all at once?

A Well, from the time we saw it at Central Vermont Hospital where the fingertips were black, **[134]** it just—it just kept moving. It just kept dying all the way up. And every time we saw her, it would be worse. And as it got worse, it got black and dark green and purple and just awful and of course it was painful. It's not like it had lost feeling. It was painful.

Q How much pain was she in?

A We—we could see that she was in pain all the time. You know, what they were giving her we didn't know. I mean those kinds of medical things we didn't have any—we weren't family, we could just be with her, talk to her.

Q Used the word dying. Was she watching parts of herself die in front of her eyes?

A Yeah, that's what was happening. And from what we heard was they were going to have to at some point make a decision of how much of the dead arm they were going to cut off. And they didn't want to operate too quickly because if they cut off this, it could still keep going and then they'd have to do—they wanted to do one surgery. That was what the doctors said.

Q So how was she taking all of this? What was going on? What were you witnessing her reaction to this was?

[135] A Incredible fear. It's so hard to describe. It's watching somebody you care about having her life altered so critically and at the same time being in such pain. The complete unknown of what the future was going to hold for her with—and then how much of it she was going to lose because she didn't have a clue, you know, how far was it going to go?

Q Did you see Diana after she got home from the hospital?

A Yes.

Q Did you make a point of seeing her frequently or was it just—

A Sure.

Q Tell us about that.

A Contrary to her entire existence before this, the one thing that struck me was one of the big decisions was what big new chair could be gotten for her to sit in. Diana was not the kind of person that sat around, but that was like a big deal, and understandable, but you know, what a difference. Here's some-

body who beforehand was like flying a hundred miles an hour and then the big decision was well, what comfortable chair could she sit in? It just—it was such a—for me it [136] was such a personal contrast of who Diana is, just that simple little thing to me was shocking. We went there. We would go for dinner. We'd take stuff. Probably a couple of months after she got home she said I want to show you something and she has a piano in her house and she got up and with her left hand played a piece. She got out a piece of sheet music and it was about 30 seconds long and she made it okay. She kind of turned to us with tears in her eyes and said there are not a lot of one-handed pieces for one-handed piano players. I mean I don't know how many one-handed successful musicians anybody has ever heard of, but I haven't heard of any.

Q You told me about something that happened at your house when you invited her over for dinner. Why don't you tell the jury about that.

A We had neighbors who have friends who come and stay from France in a log cabin on their land right on the Dog River. It's a log cabin that has no plumbing, no electricity, and these folks live there for two months every summer. They love Vermont so much they've come from France to stay here. And through a set of circumstances we

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[Testimony of Elizabeth Winn]

[142] she, being my older sister, definitely was the one to influence me. She took the piano lessons and so that made me want to do it, and she—everywhere she went and still—not still, but she would take her guitar around with her everywhere she would go, down on the dock—we grew up on Lake George—she would take it

down on the dock. So I'd follow her and want to learn how to play guitar, always wanting to do what my older brothers and sister wanted to do. So she was my main influence in music.

Q We've already heard a lot about your sister and what music means to her. I think we can skim over most of that, but you said something about your sister singing in the shower or something that I thought summed it all up. If you could just tell the jury?

A Um, well, what I said was a lot of us are closet musicians and we will sing at full voice and tilt while we're in the privacy of the shower, but for my sister, the whole world is her shower, she sings everywhere she goes. She brings her guitar—or did—everywhere she would go and she would sing and always, always, always, always composing and singing. So the world is her shower.

* * *

[144] Q You do that with one hand, right?

A Yes, but the thing that I think hasn't been said that I want to make really clear is that a lot of people say okay, she has one hand, she can still do this. But being the sister that lives next door and sees her every single day, I'll tell you she doesn't have—she doesn't have this hand a lot. She has severe overuse syndrome in this hand. She tries, as you've heard, you've heard about her perseverance. I've had to yell at her upon occasions to just put the pot down, you know, don't strain yourself. Let me do it. Let me help. So she has severe tendonitis in both shoulders and overuse syndrome. She has to wear a brace and, you know, the cold pads. And so most of the time she doesn't have either. And the prosthesis helps mostly with driving, but the prosthesis is enormously heavy and it adds to the ten-

donitis on this side of her body. And so I just want to make that clear. It's like yes, we're lucky she has the one hand and we're lucky she has the elbow, but in many ways, many times she doesn't have either. I don't know if I answered your question.

Q Well, yeah, I cut you off, but in terms of does she still enjoy painting after—

[145] A Yeah, so she still enjoys painting, but it's like everything. First of all, she has this—her left arm, which is her dominant hand is disabled as well. So it's very difficult, especially her hand, I would say it's like—it's almost like people who are crippled with arthritis, it's very painful. And so she—it's as Jessamin pointed out, the joy of it isn't there and it's so stressful that she becomes kind of this inertia and so she doesn't do it because it's painful mostly, also because it doesn't bring her the joy, but it's mostly because it's painful. She's in chronic pain, constant pain.

Q Now, you were—I had asked you about other creative things that she used to like to do before the amputation and she can't do now. And that's when I cut you off. If you could just continue on that.

A An amazing photographer. Again, just natural talent. She has an eye for composition. So she's done it for as long as I can remember. And even as a young adult, she had her own dark room with the developer and developed all of her photographs and they're just gorgeous. Just gorgeous.

[146] Q Can she still do photography now?

A Yeah, as you heard, the determination. She's determined. She's, you know, first she grieved and grieved and she would watch people taking pictures and just cry and cry and cry and "How am I ever going

to do that?" But determined she's trying to figure it out, so like she'll take her right limb and prop the camera up. I didn't mean to bring these for a camera prop, but you know, prop it up and then—and that's what happens—and then she reaches over 'cause the clicker is here and she'll click. So, you know, I bought her a little tripod and we'll play, but again, it goes back to this hand is still very painful and the effort that it takes to do that. Just the little day-to-day things she has to do like showering are all she can do. So to take pictures is just—she pretty much doesn't do it, but I know she wants to.

Q Liz, you talked about day-to-day things. Why don't we just jump ahead into that for a minute? At least in my own mind at least jump ahead. After the amputation have you lent assistance to your sister in daily living?

A Yes.

[147] Q And so you know what she can and she can't do. You've seen it first hand?

A I see the things she hides from her daughter.

Q Let's just go over some of these things. Let's start with getting dressed. Buttoning up a shirt.

A She basically can't do—I mean yesterday she was trying on one of my blouses and I noticed that I automatically was buttoning it for her. So I think she just kind of tries to stay away from outfits like that. But she can do it, but it's trying and because you have to button something, you have to, you know, first punch—most of us kind of do it like this, you open one hole and throw the button in. She has to do kind of both simultaneously. She can do it, but it's extremely painful and just frustrating. So she tends not—you

know—we buy our clothes differently. We shop together and we look for different kinds of clothes now.

Q How about putting on a bra?

A Well, I helped her with it yesterday and I help when I'm there and I know I can't go down there every morning and put her bra on, but when [148] we're together I do it for her. All I can say is try it because you—you know—it takes two hands. And to do it with one hand is like—is contorting—you know—hands and painful. It takes her I would say, when she chooses to wear one, because it's such a pain, it probably takes her about ten minutes.

Q Putting on socks?

A Same thing. It's—for most of us we it takes two hands. We open it up and pull it on and for her she has to shove her thumb in and kind of just kind of wiggle it in and it takes a good minute per sock causing pain.

Q How about putting on a belt?

A She doesn't wear a belt anymore. Again, for a belt you have to go around like this and she doesn't even bother anymore. She doesn't even bother wearing pants anymore because to put pants on you have to lie on the—it's similar like a big sock, you know, she has to basically lie on the bed and puts one leg in and stands up and puts the other leg in and again, causing pain and then the zipper, you know, again, think of it. You need two hands for that because you have to make it taut, so she'll put her elbow and then go like that. And [149] then the hooks, again, similar to a button, it just—she doesn't wear pants. She doesn't even—well, I won't share that—I won't say what else she doesn't wear.

Q Shoes?

A Shoes, we make sure she has Velcro sneakers. She can't tie at all, but again, similar thing to a sock. That to put on like rubber boots, it's extremely painful for her and takes her forever. She gets frustrated.

Q So what time do you leave for work in the morning, Liz?

A Around quarter to seven.

Q So you take much time getting dressed or are you just up and out?

A I'm up and out.

Q Take much energy for you to do that?

A Oh, no.

Q How about Diana, if she wants to get dressed in the morning and get out of the house, how much of an effort is it?

A It's huge. I mean every single step, starting from—starting from just when you get up in the morning, we think of the simple act of just making our bed, she doesn't do that. Even tucking [150] herself in at night, you can't pull sheets up.

Q We'll get to that, just okay, but getting dressed is a chore for her?

A It's a huge chore, yes.

Q Let's talk about personal care, shaving, women—how is it for her shaving?

A Well, when this first happened, I had to do it for her.

Q And why is that?

A Because she can't—can't do this. So she has a left arm so she can do her right armpit, but to do this

one, I needed to do it for her. So basically what she does now is just goes like this and, you know, just don't look on that side at her armpit.

Q How about flossing her teeth?

A For awhile she didn't do it at all and her teeth really suffered for it. In fact, I think she had one tooth that had a ten millimeter pocket and it had to be pulled. And so they found—similar to what Jessamin was describing with the fingernail cutters—it's a one-handed—it's almost like a little bow.

Q Like a violin bow?

A Like a violin bow, so she has that now.

[151] Q How about washing her hair?

A She puts the shampoo on her limb and then quickly before it falls off or maybe the second attempt, because the first one has fallen off, she just kind of quickly scoops it up and then she can do this.

Q Cleaning her fingernails?

A She doesn't do it.

Q Let's talk about some household procedures. Using scissors?

A Again, she basically just doesn't do it.

Q Why is that? I mean I can go like this with this hand.

A Because you have to hold it kind of—I'll do it with my right hand. You have to kind of hold the paper taut. And also again, that's why, you know, it's a small motor skill, scissors are in fourth grade. They're—just now they've just mastered it and so it's a small motor skill and she—this is what's painful. So it's the little

everyday things like that she just doesn't want to do, she has other people helping her with.

Q Opening the daily mail, the envelopes, you get every day?

A Again, she—I've seen her do it. She [152] gets the mail, sits down and puts her finger in, but for the most part she has help with that or just rips it apart. I've seen her use her teeth, too. She had mentioned that, that she does a lot with her teeth and she has damaged her teeth. They're all chipped in the front now. I mean like, for example, hold up a pair of pants because, you know, putting pants on a hanger, you have two hands for that. So what she'll do is put it in her teeth and go like this, so she does a lot with her teeth.

Q Can she hang clothes? Take a jacket off, take a hanger off and hang it and put it back up?

A It's one of the things that we helped her with. There are many, many things that we actually had to—it's like Jessamin said, it's like being a kindergartner, things you start over with and hanging was one of them, that she really wanted to learn how to do. And so she can do it, but it's a huge effort. So much effort that we just said, you know, it's one of those things don't worry about it. We just put some hooks up in her closet.

Q Because hanging is one of the things you have to use teeth with?

[153] A Yes.

Q Hold the hanger with the teeth?

A Yes.

Q And what about opening bureau drawers? You've got a bureau, you want to pull it out.

A Her whole house is not real expensive antiques, but farm antiques and she takes a lot of pride in them and loves them. But most of them have handles on either side or knobs and they're kind of funky. You know, the older drawers are harder to pull out, but she really loves them and so my father came and put knobs in the middle so that she can just pull it out and then it's more balanced, but we probably need new furniture.

Q Writing checks?

A Again, I've seen her do it and, you know, she's determined. She'll go like this and do the writing, but it's a lot of effort. Just a little simple thing like that where you have the types of checks that have copies to see through so she'll have to, you know, flip through them and put one elbow down and the other elbow down like this and then— and then put the elbow down, put the other one, rip it out.

Q Taking money out of her wallet?

[154] A She can't. She doesn't have a wallet anymore. She just has it loosely displayed in her purse.

Q I think you already mentioned this, changing— I'm not talking about making the bed—changing the bed. Your weekly change of the bed, stripping down the sheets, putting them back on, did she do that?

A Yeah, she's determined so she tries, but we pretty much—I—said I don't—I discourage her from doing it and she gets help with that, but she would try. And again, what's hard about changing a sheet is that, you know, when you think of the bottom sheets, it takes two hands to pull it over that corner and so what she—she just can't do that part.

Q Sewing. Diana used to like to sew?

A Yeah, I mean I could still go on with all—photography, other things like she does, but sewing is one—but yeah, sewing was one of them. She's an amazing seamstress. We got it from my mom. She's better than I am because she's more patient in general. And so we—I have many childhood and young adult—for my parents' 50th wedding anniversary, again, it was her idea—she [155] instigates all the wonderful events in our family. She, you know, everything is a party and she wants to celebrate everything so she went out without a pattern and we made these wonderful outfits. So yes, she was a wonderful seamstress, and no, she can't do that anymore. Yes, she's deeply saddened by it. She feels humiliated. I know she doesn't want to call me. She knows I'm busy, too, and she wants to protect me because I'm her little sister. She hates to call me to ask her to so something and luckily for both of us she does.

Q How about reading the newspaper, getting up in the morning, sitting in your big armchair and just reading the Times Argus, Free Press, whatever you happen to read in the morning?

A She can't do it that way anymore. She has to put it out on the kitchen table, and again, can't just sit because you have to go like this. She pretty much has to stand up to read it. She can't do it at a coffee table. She can't even really read in bed.

Q How about reading a book if she—does Diana like reading?

A She loves reading. She reads constantly.

[156] Q Good book at night, read in bed?

A No, she has trouble because, you know, again, when you're lying in bed, you have to—you know, when

you think about it, you open it up with two hands and you're reading like this and then you take your hand—you know—you take it and you hold in the middle like this to turn the page. So she would have to like put it down, turn the page or, you know, turn the page and pick it up again like that. And again, overuse. It's heavy. She basically just doesn't do it as much.

Q So she can't at the end of a long day go to bed, read a book in bed?

A Not without enormous strain and efforts and it gets her into that kind of inertia place where she's just overwhelmed. And I know like a lot of us, when we get overwhelmed, we just "Screw it."

Q She needs a table is what you're saying to read a book?

A Yes, absolutely. She can't read in bed.

Q What about unwrapping packages?

A She just rips it open, but if it's—she gets a lot—Re-Bop Records gets a lot of mail that's with that super protective tape, and again, [157] so it would involve scissors to cut the string and getting through that heavy packaging, so she basically just asks for help with that.

Q Vacuuming?

A She doesn't do it. It's just, again, the problem is that it's overuse. She has got to protect a hand that's already damaged.

Q Mopping or sweeping?

A Um, mopping really takes two hands and, you know, to put it in the bucket and then do that squeegee thing, so she gets help with that.

Q Laundry?

A Um, I've watched her take things out of a dryer, you know, a lot of us, you know, you open the dryer and put both hands in, you take them out and you put them in the basket. You know, she can do that one hand, but what she said to me this morning, she got very teary because she had borrowed some of my clothes and some of her clothes were in the laundry basket and I was just doing what I always do when I go there and kind of do a little 52 pick-up and I was taking my sweater and doing that thing you do where you take the sleeves around and fold it. And she looked at me and she had tears in her eyes. So she doesn't—she can't [158] do that. She can't fold her clothes.

Q What about folding your sheets?

A Yes.

Q Folding your linen, folding anything?

A My mother—our mother, I refer to her as a "Donna Reed" type. She—"Father Knows Best" wife, and so she has the perfect way to fold sheets and Diana last summer was determined that she wanted mom to show us how to fold sheets the right way. And, you know, I was working on it, but she just couldn't do it. I mean she can't even—so she just would, you know, again, doing the tooth thing and trying to do it. And so finally she just "I'll do it my way" and she just crumpled it up and threw it away. So no, she can't fold sheets.

Q Ironing?

A Very, very much something I don't want her doing because it's, again, that overuse syndrome of her good arm. Plus, you know, you have to take the clothes

and spread them out and usually you lay it taut and iron like this.

Q Typing?

A That was actually a skill that my father was very proud that she got in college. She's a very efficient typist, fast, and now she can only [159] henpeck. But again, she really shouldn't do it at all because of the overuse syndrome. We tried to use the voice activated typing, but they're very ineffective.

Q What about opening a jar? Opening the vitamins in the morning or a jar of aspirin at night?

A Well, you know, again, one of those things, you know, you don't think about. And even myself, I catch myself oh, whoops, sorry, I'll hand her a bottle. She'll ask me for some Excederin. I'll hand her a bottle, child protective cap, you can't do it. She can't do it. So I think the local pharmacy has special jars that they make for her, but an ordinarily going to the drug store, buying Excederin, she has to ask for help with that.

Q Does she ever call you and ask for help to open a jar or bottle?

A Yes.

Q Why don't you tell us about that?

A Well, again, that's why I mentioned the Excederin because that's the memory that I have is she had a migraine, and she doesn't get them as frequently, but when she gets them, she likes to [160] start with Excederin before the Imitrex. And so she likes to start there. And when you're in the middle of a migraine, and up—you're in chronic pain from head to toe and you can't use either arm because this one has been strained from the everyday things of the day, she'll call—she

called me up on a number of occasions, call me up and ask me "Could you please come down and just open the aspirin?" And I'll do that.

Q Let's talk about kitchen activities, going to get a paper towel.

A For her about ten come out.

Q What about cooking meals?

A Again, she's determined, and as Jessamin already mentioned, she had to get rid of most of her pots. My main concern for her is that she has a gas stove and for her to light the stove, she has to first turn on the gas, which it's an old stove so it's one of those that's heavy to turn, push it in, and turn it is strain on her left hand. And then while the gas is on, she goes over to get a match, can't do these matches, she'll grab the match from her little match box and strike, strike, strike, strike, strike, poof and, you know, goes on. Explodes at first and then—and then simmers [161] down. And same with the oven.

Q What about cutting and chopping? You need to cut an onion.

A Yeah. I've mostly—I'm trying to think—like I mostly try to see her cut meat and she'll have to ask for that—like if we go in a restaurant, she has to ask. I'll cut her meat for her. When it's just the two of us, she just picks up the steak and just gnaws on it with her fingers. Something like an onion, she just, you know, what she does is kind of props it up and tries to cut it, but it doesn't work. She—my main—one memory I have was because she loves oranges and she has to ask for help in peeling oranges and again, sometimes she doesn't like to ask so she'll peel it. But again, it's interesting to try peeling an entire orange with one hand.

Q Cooking some eggs in the morning, cracking an egg?

A She's got it down pretty well okay now, but it took practice and it still can be sloppy, but that's one of the things. And Jessamin talked about how joyous she gets when she can do the little things. She practiced and, you know, and now she can do it okay, but it's messy, and again, **[162]** it's a fine motor—it's—this adds up after the day, little things like that.

Q Buttering bread?

A Again, bread, it just—she has to make, you know, it gets all kinds of broken apart when she butters that. Toast—toast sticks, usually even that she has to put the toast down and do this and—or she'll take the butter and kind of like this, but it's hard and, again, it's the little things that add up. By the end of the day—by the end of the morning—she's really pooped.

Q Washing dishes?

A Again, a lot of strain. How she does it is she has one of those wands that have the little scrubby on the end and she'll put the pot in the sink and run the water and just scrubby, scrubby, scrubby. You know, the pan's kind of going around and so she can't really get at the grunge. She always tells me she used to judge other people for their coffee cups, you know, because they didn't get the grunge and they're gross. Now all the coffee cups have that grunge in the bottom. What other trick she does to wash cups and things is—or to dry, for example, is she will actually use **[163]** this and, you know, whoops, that's filled with water, kind of gets in there to wash, too. But it's hard.

Q Just been talking about daily activities. Haven't gotten to creative activities or athletic. So doing

all these things we've been talking about, how do they end up leaving Diana during the course of a day?

A Again, in a way I'm not used to seeing her—she's extremely—she tries so hard, and she's so determined, but she is so exhausted. And the part that I see that she, you know, the other people that see her on the streets say Diana looks so good, and she's determined, and she's a go-getter. All of that is true, but she also is deeply exhausted and in excruciating pain and just—it's overwhelmed. And then that still inertia place she gets frozen, just like with this look of panic and despair. And I'm trying and I can't do it and she's exhausted and frustrated and depressed.

Q So does Diana need assistance for doing these daily activities?

A Absolutely.

Q You've been providing that assistance?

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[165] Q Now, we were just talking about the mundane things we all do to get through the day. But recreational things, what kind of sports, if any, did Diana like?

A Um, as a family we're always into downhill skiing. We grew up with that and then moving to Vermont of course we did that together. Charlie and Diana and myself, the three of us, would go over to Stowe and she loves it.

Q Can she still downhill ski?

A She tried it once. She went over to Sugarbush to take advantage of a—

Q I'll help you out, the adaptive program?

A Yes, adaptive program and, again, that determination, she was all excited. She was going to try this and bring skiing back into her life and make sure it would continue, but she had a couple of spills and it hurt and she just decided, you know, she's got two good legs so better not—

Q Is that something you and Charlie still do every Sunday at Stowe?

A Yeah, we do and it's, you know, I feel badly we leave her behind, but I still do it. Charlie—

Q Cross-country skiing, did Diana enjoy [166] that?

A She loved it. Where we live out in Marshfield I have 55 acres of land and she has over 20 and we have gorgeous cross-country ski trails that are maintained by our neighbor and that are private and so we're really lucky and so we went out all the time, at least once, twice, three times a week. And I try to get her to go, but it's hard with cross-country skiing, you really do need the poles.

Q That's a real upper body sport, cross-country skiing?

A Yes, it is.

Q What about tennis?

A Something she always loved to do and, again, I'm seeing a big umbrella with everything she loved to do involved other people. She's a very—much more than I am—a people person and so very social, so tennis was something that she liked, skiing and cross-country skiing, tennis was something that she loved to do, plus she loved to do it with her friends, so she did it with her

friend Susan in Boston and with her husband Crow and it was a social event.

Q Can she still play?

[167] A No. No way. I mean you think, okay, got one good hand, that's all it takes, but there is no way she can do that with her overuse. Absolutely not.

Q What about just backyard games, croquet, badminton, things like that?

A We group up in Lake George so we played summer games of badminton and croquet and, again, she still tries, but I can tell because I know her, that it's that part of her that's determined and she's wincing with pain. Croquet is harder, you really do need two hands for that. You have to steady the—so we just took the—we just took it away. We have the net up, but we don't play croquet anymore.

Q I forgot to ask you about a couple of maintenance things. Just yes or no. Can she mow her own lawn?

A No.

Q She used to do that?

A Yes.

Q Shovel her driveway?

A No.

Q Shovel her walk?

A No, I do that.

[168] Q Rake her leaves?

A Not as often as I should. No, the leaves are left. She can't rake. That takes two hands and—and even if you could figure out a way to do it with your

one, which—see, I tried all these—I've tried everything with one hand. And as she puts it, it's not just one hand, it's one hand tied behind your back because, you know, the rest of us, when we try to do one hand, you have balance and she doesn't have that balance. So I tried to do that and it's just—it's hard, it's two-handed.

Q Did she used to do that stuff or was Diana the type that hired everything out?

A No, no. I mean no, she was never the gardener that I am, but she always kept her lawn mowed and raked.

Q I said I wasn't going to talk much about music because we've heard a lot about it. I wanted to ask you about—you've heard the testimony about music and the importance of it in your sister's life, correct?

A Yes, yes.

Q Heard that today?

A Yeah.

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[171] important were her hands in terms of that involvement with kids?

A Well, we saw her. I mean she was, you know, pointing with her nose and, you know, directing everybody. And, you know, we talked already about the instruments that she used which was a huge piece of it. You didn't see in that particular one, but she used that, too.

Q Liz, we've gone over this with some other witnesses so I don't want to spend a lot of time on it. After Diana got her shot of Phenergan before she went up to CVH, three or four weeks later, she actually stayed at your house that time?

A Yes.

Q Tell us what you witnessed.

A Um, while she was at my house?

Q Yes.

A Starting there? Excruciating pain like I've never seen in my life. I mean the hand itself was mottled in blue and swollen as people have said, but for her it was just excruciating pain. And the way she, you know, she's a quiet person so she'll express that pain just kind of wincing. And as Jessamin said, sounded like, you know, the groaning and moaning, but just horrible, horrible, [172] horrible, horrible, horrible, excruciating, excruciating pain. So she was given, you know, drugs to—painkillers to monitor that. And I remember once, I think it was Percocet, but I'm not sure, I remember once calling up to see how she was doing. I think I called from work and she answered the phone and she didn't know me and she—she just was in excruciating pain and had to manage it with intense amounts of painkillers. She was beside herself with pain, unmanageable pain. I don't think words—I don't think I can find words.

Q After the amputation, when Diana got home, how was it at first?

A She just was like a child coming into her home and, you know, surrounded by family, but she was just kind of walking around in a daze, but again, the part of her that everybody has shown us I think is the determined part, too. She's glad to be home and tried to make the best of it and, you know, started immediately trying to see what she could do with one hand, but spent most of the time, you know, especially, as I said, when Jessamin was around just really trying to buck up

and—but for the most part, just kind of spending a lot of time [173] trying to manage the pain and depression, you know, big depression unlike I've ever seen in her.

Q Much crying?

A Yes. Constantly.

Q By Diana?

A Yes. And by all of us, but yes, by Diana. Lots of holding each other, just crying, grieving. I mean—

Q So your strong, big sister, what kind of shape was she in?

A She was very weak and she was always, you know, again, I—she was always really strong to me and our symbol for her is Diana the huntress, which is Diana the Greek with the arrow and that was always her symbol and she has that all around her house. And now she was, you know, weak and very fragile and I had never seen that before.

Q What about her body image? How did losing her hands affect that?

A Well, they say you're as pretty as you feel and she didn't feel very pretty. So she I think felt a lot of shame and embarrassment. She assumed—sometimes wondered—but a lot of times assumed that people would be kind of uncomfortable around it, especially the children and especially [174] men. She—she just, again, confided to me as her sister that she assumed no man would ever want her ever and she still struggles with that. And then children, too, she really was worried with Re-Bop Records that working with kids, that they would be grossed out by her because kids tell you how it is. And, you know, so the stares and all that she

still gets the stares and she's very self-conscious of them. Ironically the kids have been the best.

Q You mentioned the word depression. I mean it's four years later. Have you witnessed constant depression, intermittent depression? Has it subsided? What have you seen?

A Well, I guess I have to say intermittent because she definitely is Diana and she carries her spirit wherever she goes and the essence of who she is is a go-getter and determined. She still has that huntress spirit, but it's more frequent than I've ever seen before. I would say that she is—what she is constantly is overwhelmed. Every single thing just completely overwhelms her so—so it's a mixture of overwhelmed and panic and depression weaving in and out. But the depression is always there. It's always—it's always there like peripheral vision. It's either here for her

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[176] because it's such a part of who she was. Her husband was her soulmate and her business is her heart path. John talked about that. But as her sister living next door, it terrifies me to think of her having to let go of that business completely.

Q You—Diana used to like to swim?

A Hm-hmm. Still does. Again, we grew up on Lake George and she, being older than I am, grew up on other lakes and rivers, so we've always been swimmers, all of us. We just jump off the dock and I tend to be more of a lap person, I go out and do my laps, and she likes to kind of just swim around. And first time she came out with her limb in a bathing suit, which was very hard body image for her to come out in a bathing suit.

Q This is the family's place on Lake George?

A Yes, on Lake George. Out on the dock. It took her a few days to put on a bathing suit and it took me, too, and her family to tell her she looked beautiful. And then she—once she decided to put on the suit and get out there and, again, there was that Diana part again and she went—we're all kind of like "Do we swim? What do we [177] do?" And she just went in and so we all went in and we're swimming and I'm doing my lap thing and I turn around and she was going in a circle—she didn't realize it at first because she was trying to do the crawl but, you know, doing this and so she just was, you know, going like this. And so she still swims, but it's mostly the breast stroke and she can do it, but—

Q What does that tell you about Diana?

A She's—again, she's Diana. She is—aside from my mother, the best person I know as far as goodness. Good heart. Again, she's my model. I have a lot to learn about goodness and she is my model and patience and determination, acceptance, you know. She just—she sees the good in people. She sees the jar half full and she's my model for that.

MR. KIDNEY: Thank you, Liz, I don't have anything else.

MR. O'ROURKE: We have no questions.

THE COURT: Thanks, Ms. Winn.

THE WITNESS: Thank you.

MR. RUBIN: We have our last witness for the day. We can take a five minute break or we can keep plugging along.

* * *

[Testimony of James Rosen]

[184] that her professional life was really her self-identity. And finally, I think her lifestyle before her injury showed that she was a very well-rounded person, family oriented. She was into the outdoors, had a lot of friends, strong, romantic relationship and that she really had diverse talents and interests in life.

Q And after doing everything, Doctor, what did you—let me ask it this way, has the loss of Diana's right arm, right hand, and right forearm in May of 2000, did it cause her any psychological problems?

A Yes. She has a major depression and post-traumatic stress disorder and a body image disorder.

Q Okay. I'm going to talk about these psychological conditions, but before we do that, if you could tell us how the amputation affected Diana's functioning. And, again, we've already heard of this, but I think it's important to your evaluation so if you could just touch on it, let's start with work.

A Okay. Well, from a psychological point of view, I think as Diana tried to explain that her guitar and her music—her guitar concretely—

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[190] being very physically attractive and energetic and dynamic. And I think to the point that when you looked at her performance, you recognize that her physical appearance was—it was like a professional tool that she used in her work. And so it's not surprising that she has a lot of concerns about the changes in her appearance and how people react to her.

First on a professional level, there's a concern how are kids going to react? And she's had a lot of fears of repulsing children or scaring children or turning them

off. She has kind of conflicted ways of handling her amputation around other people. Sometimes she is sort of defensive and she'll tell the whole story about how it happened. And she'll allow somebody, maybe just an acquaintance, to see her prosthesis or her stump and sometimes she will hide herself and avoid the topic. Or worse yet, not go out and function like not going to social events or not wear clothing or something that might reveal her deformity.

Q So Doctor, your clinical conclusion after interviewing Diana and looking at all of the material provided to you is what?

A My conclusion is that Diana is an [191] intelligent person who is trying very hard to cope with her condition and she has a lot of strengths and a lot of courage, but nonetheless, despite her positive attributes, she does have depression, post-traumatic stress disorder, and a body image disorder.

Q And the tests that you conducted, the MMPI, and the interview of the standard clinical interview technique, did these support the conclusion that you've just offered?

A Yes.

Q And how so?

A For example—well, the structured interview shows that she meets the criteria for a major depression, meaning she has significant depressed moods, and I'm not talking about just the normal blues like everybody gets, but, you know, painful feelings of depression and then overly negative attitudes about herself and her future and problems in motivation and energy level. The MMPI, which allows you to compare the patients with people in general showed that she scored at the

96th percentile on depression, meaning that compared to ordinary people, only four percent of the population would score higher than her on [192] depression. So she was definitely in the clinical range in that area.

Q In terms of depression, what are her symptoms then?

A Depressed moods, most of the day—most days of the week, loss of motivation, some problems with weight maintenance. There was a time when she slumped into a deep depression and lost too much weight and her prosthesis didn't fit her; problems in concentrating and making decisions. There was a time when she had death wishes. Those kind of classic symptoms of depression.

Q Doctor, could you just in everyday terms, like you were talking at the kitchen table, tell us what it means—what does it actually mean when you suffer a major depression?

A Well, I think one way would describe it is that it's a feeling that really hurts, you know, that you feel sick to your stomach inside, achy, hurty. And then there's the whole attitude that goes along with it, which is that things seem so bleak that you can't imagine things better and that whatever bad is happening to you now is so bad that life, you know, might not be worth living.

Q What about antidepressants? Diana is on

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[203] surprising. You could predict that her depression would continue and maybe even get worse.

Q So Doctor, do you consider Diana's psychological conditions with respect to depression, post-traumatic stress disorder, and the body image disorder,

do you consider these to be permanent or will they be resolved sometime in the future?

A Well, I don't see them being resolved anytime soon. These are problems that are going to continue and that's largely because the stresses that cause these kinds of problems aren't going away. She'll forever have to face her disability and the impact on her lifestyle and career and relationships. Those aren't disappearing, so she's always going to have some ups and downs in her mental health. Her post-traumatic stress disorder, you know, although she might be bothered less by it at some times, will not go away because, you know, she's not going to forget what happened to her and she has this constant reminder. So these are persistent problems that she'll have to learn to deal with.

Q Permanent?

A Yes.

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MARCH 10, 2004

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[Testimony of Dr. Mark J. Bucksbaum]

[33] Phenegran intravenously.

Q I'm going to interrupt you because what I would really like to do is start with Dartmouth because I think we've heard this several times.

A Okay. It came to be that as the necrosis of the hand or the injury to the hand progressively worsened, that they decided that the limb was—the survival of the limb was threatened, and at that point she was transferred to a higher level facility, which was the Dartmouth facility, to try to address saving of the limb.

Q What was going on with her hand medically—physically?

A At that point the hand was becoming necrotic, it was pre-gangrenous.

Q Let's stop there. Necrotic?

A It was dying. The tissue itself was turning—was initially red and it goes through a transition where it ultimately becomes black and there are transitions of colors between that, but it's—essentially the limb is 'failing to survive. It's not getting the nutrition that it needs and the tissue starts dying off.

Q Gangrenous?

A Yes.

[34] Q What is that?

A That's the next stage after the necrosis. It's when the tissue starts to literally break down and there becomes liquidification of the tissue. If it's left unchecked, becomes a life threatening event where it can progress further up the limb. The prospectus is to try to save as much of the limb as possible. This is looked at first through a viability of the tissue and there has to be a clear margin of tissue where we believe that the limb will survive or what's left will survive.

Once that's determined, the next consideration is how many joints can be saved? Each joint in our body represents function or more function if we save it. So decisions are made to try to preserve as much function as possible by saving as many joints as possible. In this case the initial attempt was to try to save the wrist, and that was the first procedure that was performed was an amputation to spare the wrist. And unfortunately, over the next several days the condition wors-

ened and it was felt that they needed to go and do a revision where they had to go above the wrist. At that point sparing the elbow was the major concern. And then the other consideration is [35] having the optimal leverage to assist using an artificial limb. Too long is not good, it creates a problem. Too short creates the same problem the other direction. So there is an optimal distance that we would like to have when we're making those selections.

And that's what was considered in her case, where she ultimately went on to have an above the wrist or below the elbow amputation.

Q Was she at risk of death?

A Yes. As I mentioned, it's a fairly serious situation. The tissue is dying, the vascular supply to the area has been compromised.

Q Vascular supply?

A The arteries and the veins have been compromised. Because of that one of the medications that she was given were blood thinners. The reason for the blood thinners is to prevent clotting or further worsening, but if an individual gets a clot, that clot can then move up through the arteries and it can create quite a bit of problem for the lungs and for the brain. And it is an extremely serious risk for which they did take it seriously and tried to medicate her to prevent that. That's also—part of the decision in going [36] to an amputation is to sort of minimize the potential damage or the long term risk.

Q So the amputation in a sense is to prevent a risk of further damage or death?

A That's right.

MR. RUBIN: Your Honor, there are five photographs of the hand that I mentioned to the jury. I'm going to start—and they've been admitted by agreement previously. Could we see Exhibit 41 please?

THE COURT: All right, so 41 is admitted by agreement.

MR. O'ROURKE: Yes, your Honor.

THE COURT: Just so we get it all out of the way, what are the other numbers?

MR. RUBIN: By agreement 41, 27, 28, 39. And what do you have in front of you? There is a number on the back.

A Forty.

MR. O'ROURKE: We have no objection, your Honor.

THE COURT: Twenty-seven, 28, 39, 41, and 40 are all photos and are all admitted.

A The first thing we notice is the markedly swollen limb, which is the body's healing [37] response.

Q Let me just put the time frame on this. This is April 30th?

A Yes.

Q And I think she went to Dartmouth the 26th of April, so this would be four days after admission?

A So what we're seeing is the redness, the marked swelling. There is a—what we call a demarcation line. There is a essentially a margin that you can see through here. The physicians have put some dots there. I think you can see from here, showing where the current line is. Essentially we're doing this so we

can monitor the progression of this. This hand is in considerable jeopardy. As you can see, it's a very deep, dark purple color. The fingers are markedly swollen. In this view we can't see the fingertips, but the hand is becoming necrotic, which is a process that starts down at the tips and is going to—as we can see further on—move up the limb as we go.

Q Let's have the next picture.

A This is another view. We can see again the demarcation lines. The fingers, again, are markedly swollen, deep purple. Here we can see the [38] nails are black and we can see that the blackness is extending up into the tissues of the fingers. And this is an ominous sign for the hand. At this point they're still aggressively working with medication management in terms of limb salvage.

Q You had talked—you're an expert in pain management?

A Yes.

Q Obviously this hurts, but can you describe the level of pain that's associated with this kind of condition?

A Um, this is one of the examples that we use when we establish a pain scale. Pain scales are usually run from one to ten. This is a ten and it is extremely painful. There is a chemical reaction that's going on in the hand that will essentially put the nerve endings on fire and there's not much worse than this type of scenario.

Q Next one.

A What we can see now is that first these were the original dots that we had talked about. This has

progressed quite a bit up into the hand. This discoloration that you see now is markedly necrotic tissue. This —essentially this hand is pretty much at jeopardy. It's extremely unlikely [39] from this stage that this is going to turn around with just medications. And you can see that this now—that really dark, almost black in color is progressing up into the upper part of the hand. The demarcation line is a couple of inches higher than where we had previously seen.

Another view showing the same thing. The extension above the wrist again is a very ominous thing for us. You can see the darkening of the skin. While there's some viable tissue in here, all of this on the outside of the hand and the thumb are really nonviable at this point.

Q What about—seems to be moving up into the forearm?

A Right. And that's what I was saying. Once we —remember, we're talking about preserving function by joint levels. So once we've moved across the wrist, this is already a very poor sign for us. And at this point the surgeons are clearly concerned whether or not they will be able to save a wrist or not since it's already jumped over.

Q The fingers seem flat. Have they lost their fullness there?

A They have. This is part of that process where I was talking about where the tissues [40] actually are liquifying. They're losing the muscle mass and supporting structures. The bone is dying off and so in this view we can see the distance from here to here is very narrow. That's the side of her finger. She's lost a tremen-

dous amount of volume, which again, is essentially an unrecoverable point for the hand.

Q Let's turn that off. Thank you. Go back. We heard quite a bit from Diana's sister yesterday about loss of function on a daily basis, but I would like you to talk about it as a professional about the impact of the loss of her arm on the activities of daily living.

A Um, it's a major loss in function, as I'm sure you can all imagine. But simple things such as like buttoning a sleeve become impossible without having both hands. It's extremely difficult for her to do basic dressing, just putting on clothes, belts, socks. These are the everyday sort of things that we have to do. Just tucking her shirt in often requires both hands as an assist. Even for her to put on her prosthesis is a real problem because she doesn't have two hands to manipulate the device.

So even though it's a device that could [41] potentially help her, it's an effort in and out of it and we'll perhaps go over that some more later. Just basic personal care, brushing your teeth, combing your hair, hooking your bra, all of those kinds of functions are markedly impaired by it. I think one of the biggest issues for her was that she was a professional musician and needed to have both hands to play her guitar. And so the loss of the limb essentially took that task completely off line and now she's being slowly retrained how to sort of reapproach that. But it's—it's heavily impaired for her to do that.

She liked to work with clay; obviously that's a bimanual task and extremely difficult to do when you're one-handed and not particularly supported through adaptive equipment such as prosthetics.

Just basic things, cooking; you can all imagine the various cooking tasks, stirring, mixing, pouring. It all becomes a big problem for her, one in which she has to rely on her remaining limb to do, which is—it's quite difficult.

Q Let's talk about pain, and it may also relate to functionality here in this conversation. Does she have pain today and subsequent to her [42] release from the hospital as a result of the amputation?

A Yes. A fair amount of it.

Q Let's talk about her phantom pain or phantom hand first.

A There are two different pains, three if you're allowing for emotional pain. But there's the physical pain, which is the pain that you perceive right at the tissue. When I showed you the hand and we saw the fingers dissolving, in essence that's the immediate physical pain that's there. There is another type of pain that happens in loss of limb, which is called phantom pain. Phantom pain is a disharmony between your brain's model of your body, your body's image of itself, and what's really there. So that your brain still thinks you have a full hand, your reality is it's gone. If you close your eyes, you can still see your hand there. You can even feel the fingers moving. That's not painful. That's phantom sensation, but when it becomes painful, there's literally an electric or burning type pain in the fingers, in the part of the hand that are no longer there, but it's on fire and it's extremely painful and it travels up the arm to the brain.

[43] The body has not adjusted to the loss of the limb. Even though those nerves are not there, the pain is incredibly intense and extremely difficult to treat.

Q Diana has described some feelings of—in addition to that—some numbness and tingling feelings in the hand that's not there.

A That's already good. That is—sort of an in-between stage when some of that burning and pain is starting to calm down a little bit. You're still left with this electric like feeling, with a numbness. It's extremely distracting at best, if not completely painful.

Q Does she have any problems with her upper body, her back, neck, musculature as a result of this?

A Yes.

Q Did she have any problems with her back, neck, muscle pain before this that you were able to determine?

A Not that I'm aware of.

Q Okay.

A First and foremost, energy of our walking is combination of the whole body event, including swinging of the arms. We conserve energy [44] by using the arms in a pendulum fashion which brings momentum to the upper body and helps propel us forward. When you lose a limb or part of a limb, you've disturbed some of that momentum. So just on the most basic level, it costs her more energy to go across this room than it would have had the limb still have been there.

There's other issues which is just the weighting factor of the limb, the balance that the limb brings to us that you lose. And when you don't have it available, other muscles have to come into play to make up the difference. Ultimately that creates a strain pattern and an overutilization, which transmits some of those forces to the other side of the body and the body will do its

best to accommodate that. But at a certain point, if it becomes unable to cope with it, it is an overwhelming of it and we end up with new medical problems in these areas as compensation.

Q Problems like what?

A Well, particularly you can have strain across the neck and you can develop strain and tendonitis patterns, which is exactly what she ended up doing.

[45] Q Does she have a problem with tendonitis in her remaining hand and arm?

A Yes.

Q And how serious is this?

A Well, it's quite serious. There's been flare-ups of it as time goes on. When it gets severe enough, it brings her only remaining limb off line because at that point it needs to be rested. One of the—

Q What does that mean off line, needs to be rested?

A She can't use it. And so when—you'll see later with her life care plan, there were separate tracks in that plan, but one track is to consider what happens when she can't use her remaining arm when it is flared up. It's prone to flaring up because it's being greatly overutilized since she doesn't have the original limb. The problem is that the courses of treatment for—

Q I need you to talk a little more about what actually is going on in the arm that's causing the pain. What is the tendonitis exactly?

A Well, tendonitis is initially set up by a strain, overstressing of the muscles and tendons in the limb. And that is happening because she has [46] to compen-

sate for the loss of the other limb. If it's taken too far, the body produces an inflammatory response, which then becomes the "itis" in the tendonitis, which is the inflammation of the tendons. That in its own right is very painful. Can become chronic. One of the mainstay treatments is to inject it—which you can imagine would bring tremendous concern to her. So that's not a treatment that we can use for her. And primarily the mainstay treatment for her is to rest the limb and let it calm down.

Unfortunately, we're heavily dependent in the plan that she could use that limb to do certain things for herself. When medically she's told not to use the limb, she looks like a bilateral amputee because we've taken away both arm functions at that point and it leaves her a hundred percent dependent on other individuals or she has taken to using her teeth as a way of holding, which is not necessarily a desirable thing to do, but it's out of desperation. If you can't hold it with your hand, then you hold it with your mouth. This has its own problems.

Q Does she have to limit what she does with her good hand to avoid disabling herself?

[47] A Yes. Repetitive use of the remaining limb is going to aggravate this sort of underlining lingering tendonitis. Tendonitis has never really gone away. Its intensity changes based on her activities and also tends to fluctuate with weather so she has to preserve it as much as possible, which means that you have to kind of pick and choose your battles. Where are you going to push the limits a little bit and the rest of the time rely on devices or people or other parts of your body to make up for it?

Q We've heard from Dr. Rosen, the psychologist, who evaluated her. Did you review his report?

A I have.

Q I'm going to ask you some questions about how all of these conditions affect her ability to work. Is that something that you do as part of your profession?

A Yes.

Q What are you doing when you try to assess someone's work capacity?

A Well, the bottom line is are their injuries compatible with their original work? And—or any work? And then to make some

* * *

[51] A Just give me one second to turn to the report.

Q He testified he did an MMPI and showed her in the 96th percentile.

A Yeah, which is very severe. Just looking for the actual numbers. Just give me one second. In the scale that we use, which is moderate to marked was the level that she came out, which is the second from the highest.

Q That's on your own evaluation?

A That's correct.

Q So it is your opinion that she does not have the capacity to hold a full-time job?

A Yes.

Q And what about a part-time job?

A It's very limited to what she can do. The—in particular, she has tried to work with the guitar and tried to reintroduce this. It's really not gainful. The

amount of time, the lack of precision, it's stifled at best to the artistic process, but just from a mechanical process, it's so fatiguing and draining on her that after a couple of hours, she's really too tired to continue.

The medications also play a role in that.

* * *

[Testimony of Myron Smith]

[110] Q What is your assessment of her ability to obtain gainful employment?

A My opinion is that Diana does not have the capacity to engage in gainful employment.

Q Full-time employment first.

A She absolutely does not have the capacity to engage in full time employment.

Q Why not?

A All of the resources that we discussed, psychological, the medical, the vocational evaluation by Easter Seals, the functional capacity data, all indicates that she has number one, a less than sedentary physical capacity, and she doesn't have the capacity to sustain work activity productively, work activity for substantial periods of time. Now, plus at age 55 or older the Social Security Administration, who's been at this for decades, defines us as persons of advanced age. When we reach that age category, our transferable skills, those skills that we've acquired in past work need to be directly transferrable to a new job. We aren't very successful in teaching older folks to do new things when they have the addition of a handicapping condition. We just simply aren't. **[111]** So when I took a look at the 72 worker characteristics that the federal government defines every single job in the United States economy

practically with these 72 worker characteristics, we looked at Diana's prior work history. What is it that she did? We looked at what are her residual capacities? And we tried to match these up. And as wide of analysis as I did, no jobs were identified in either the Vermont or national economy for which she had the residual capacity to perform.

Q Forty hours a week?

A For 40 hours a week. For one hour a week. She had no transferable skills that would meet the worker characteristics of existing jobs. Now, that doesn't mean she's unemployable. What it means is one would need to find what we call a benevolent employer who would be willing to allow her to work on her schedule, probably two to three hours a day every other day, take time off for medical appointments, missed time due to medical conditions, exacerbation of the other arm and bring to the work site a very limited skill base. So to that extent those employers for the most part don't exist and they certainly don't exist when you're 55

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[Testimony of Allan Stuart McCausland]

[143] present value using the one and a quarter percent the same way. We then sum up the present value. And so relative to the arms, we have a present value cost of $372,287. That's the amount that has to be set aside today in order to cover these expenses.

That exact same methodology showing you in those two was done for each one of these categories within the life care plan, each item that's—the 372, there is the 103. I did it for each one of these items and we end up with a present value cost of the life care plan, to provide for the needs of the life care plan of $1,280,266.

Q Do you have a summary?

A This is a summary of all of the present value of the economic loss, 725,532, and the present value of the life care plan costs of $1,280,266, and then we end up with a total present value for the cost and the economic loss of $2,005,798.

Q Do you believe that these numbers are correct to a reasonable degree of economic certainty?

A Yes, I do. I don't have any reason to doubt them at all.

* * *

[Testimony of Diana Levine]

[163] pretty much out of my mind with pain. And completely disoriented and just about as bad as a migraine can get.

Q And where did they ask you—or put you?

A They took me into a room and they are very familiar with my situation when it gets that bad, how to treat me and, you know, I have a cold cloth and I have something to throw up in and I have the lights dimmed because I'm very sound and light sensitive and—

Q Did Jessica tell you she was going to give you some intravenous medication?

A Yes.

Q Do you know how long it took her to administer the medication?

A Not really. I—I was so out of it I don't have a strong memory of that.

Q Who would be in the best position to know how long it took?

A She would.

Q If she said it was more than two minutes, do you have any reason to doubt that?

A No.

Q At some point did you feel some severe [164] pain?

A Yes.

Q Do you know how long before you felt the pain that she had been administering the medication? In other words, did it happen right at the beginning or along the way? Do you have any idea?

A No, I mean listening to the testimony and seeing the tubes and everything, I realize there's a whole big process to it. And I was so out of it, I really had no consciousness of that, like when it happened, because I was like this—with the head covered with the rag anyway. But I know that it hurt.

Q Now, were you asked at one of these depositions to repeat or say what you said when it hurt. Someone asked you to actually speak as you remember speaking then?

A Yes, yes.

Q Why don't you do that here and tell—just kind of the best you can tell us what you said in that examining room when you felt that pain.

A "Ow, that really hurt."

Q And it did really hurt, right?

A (Witness nods.)

[165] Q Did it continue to hurt?

A Yes.

Q Did you say anything after that initial statement?

A No, because I knew that it was going to end.

Q In other words, she said "Hang on, it's going to be over"?

A Yes, yes.

Q The next six weeks, we've heard from your sister and your daughter and Steve McArthur about that experience, and I don't want to belabor it, but how would you characterize the three or four weeks before you went to Dartmouth and the five weeks—I guess more than six weeks—five weeks you were at Dartmouth?

A From when it happened to through when I was at Dartmouth?

Q Yeah.

A Um, it was progressively the most excruciating pain I've ever been in. I've never experienced anything like that and hope I never have to again. Friends of mine said they didn't—by the end of it, didn't even recognize me and evidently I didn't recognize them and that's how **[166]** out of it I was between the pain and the morphine. And I was terrified. I guess that would characterize it, just like in horrible pain and terrified.

Q How long were you terrified?

A I was terrified the whole time but I was just doing everything I was told and feeling like I was going to be okay. But when I got to Dartmouth I think is when it really became clear to me that this was a life or death situation.

Q And you went through two amputations?

A Yes.

Q Since your discharge from Dartmouth have you suffered any pain as a result of the amputation on an ongoing basis?

A Yes.

Q All right. We've heard something about the phantom pain. Why don't you tell us about that first.

A Okay. I've become an expert on phantom pain. What it is is you feel like you have a hand, even if this is off, and I'm looking at my cut off limb, I still feel like I have a hand. My brain just doesn't get it. It's a huge hand like a Mickey Mouse hand and the fingers only go about

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[200] Q Yes, page 117. It starts at the bottom on line 25 and it goes over—

A "After she asked me—after she told me about giving it IV would work more quickly"—after that?

Q Let me get it for you.

A Okay. Okay. "What did Jessica say to you regarding this treatment after she answered your question that by giving it IV it would work more quickly or words to that effect?"

Q And your answer was?

A "Okay, the next thing she said was after I"—oh, wait a second. After I—something's missing here.

Q Does it say "After I screamed"—

A No, I don't—oh, okay, you go up there. "She said—the next thing she said was after I screamed, when I said—when I yelled 'that really hurt' what Jes-

sica said is something to the effect of 'it's supposed to burn. This medicine burns. You need to hold still so you don't disturb the needle.' So I held still."

Q And that was the fact of the matter as you recited it back in May of 2001?

A These are the words that I said. I know [201]—like I demonstrated earlier—that I didn't scream and it looks like I corrected myself here. When I screamed, I said when I yelled, that was my version of a yell, which is probably even more than what it was because when I have a migraine a yell is really a yell from inside my head because I'm in so much pain and I'm sound sensitive. So if what I said earlier when I said "Ow, that really hurts," if that constitutes a yell, then that's what it was.

Q Was it also one of the most intense pains that you had ever felt?

A Um, to that point, yeah.

Q And look at—did you say in that deposition—look at page 121 on line 22.

A 121, 22? Yes.

Q It was like your arm was going to explode in pain?

A Yes.

Q And when you did tell Jessica, you said it in an elevated voice, did you not?

A Yes, the way I said it earlier.

Q And if you look on line 16 of page 121—I'm going to try to stay right with the same deposition if I could. Did you tell the examiner [202] that it was "one

of the most extreme pains I've ever felt"? Isn't that right?

A On line 21?

Q Line 16.

A Line 16, yes.

Q It says, "It was one of the most extreme pains I've ever felt"?

A Yes

Q Now, on page 121 did the examiner also ask you as to what area of your arm felt the pain? From where to where? And look at page—at line 23.

A Okay.

Q Is that the question that the examiner asked you, what area?

A Yes.

Q And on line 25 what did you tell him?

A "Definitely my forearm. I don't remember it being up here."

Q So it was from your elbow down, was it?

A Yeah, I just remember it—

Q The pain—

A Yeah.

Q —was from the elbow down. And if you look at page 122 on line two, did you tell the [203] examiner that it was nothing above the elbow, that the pain was below the elbow and down?

A I said that—as far as I remember I said "I don't remember anything above the elbow, but this is the memory, the lower arm from here down."

Q And the examiner asked you if you felt any discomfort in your fingers on line five there at page 122?

A Yeah.

Q What did you tell him?

A I said that "I didn't isolate it." That it was just from here down, which would include the fingers.

Q Then when I was asking you some questions, and I had the benefit of this deposition, you remember when you were there?

A Yeah.

Q But we'll go to the questions that I asked you now so we won't get mixed up, and that's the deposition that was taken about 30 months later. It was taken November 13th or November 23rd?

A Thirteenth.

Q November 13th, 2002 at Mr. Rubin's [204] office. Go to page 33 of that deposition if you could to line six.

A Okay.

Q And I asked you just above that, "What happened, if anything, during the time that Jessica was infusing the medication into your anatomy" And on line six what did you tell me?

A I said "That's when I—that's when extreme pain occurred."

Q And I asked you then on line eight, "And did you raise your voice and tell Jessica that it hurt and it

was a burning sensation?" And what did you tell me when I asked you that question?

A I said, "I didn't say it was burning. I said "Ow, that really hurts.'"

Q And I said "What did she say?" And what did you tell me? Line 13.

A "She said—these aren't the exact words, but something to the effect of 'It's the medicine. It's supposed to burn, so just hold still so you don't disturb the needle.' That's my memory of what she said."

Q And then I asked you whether or not—on line 18—"At any point when you said that it was burning, it was hurting, did she stop infusing [205] it into you?" And what did you tell me as to what she did, whether she stopped infusing or not?

A I said that "It didn't—I didn't get the sense—I didn't get the sense that she stopped infusing me. But what I remember is that when she told me to be still, I held still. And it didn't seem like it lasted that long so I was relieved about that."

Q And then I went on and said, "It didn't seem it lasted that long. You mean her infusing the medication into your system? Into your anatomy?" And what did you say?

A "Yeah."

Q And I asked you on line four, "Can you tell me how long you think it took for her to do that? From the time she started until she ended?" And what did you tell me?

A I said, "It seemed like maybe a minute or so. Again, it's hard to really—'cause my perceptions were so influenced by the amount of pain I was in."

Q And then I followed that up by saying, "All right, but a minute is your best judgment to date?" And what was your answer?

A I answered "Yes."

* * *

[208] Redirect Examination by Mr. Rubin

Q Let's go back to—got your pages all over the place.

A It's just like home.

Q See if I can help you here.

A Yes.

Q We want to find page 118 wherever that is.

A Okay. Of K or L?

Q K. It's got four boxes on a page, your Honor.

THE COURT: Yeah, it's the scrunch thing.

Q Here it is. Now, what I want to do here is start on page 117 at the bottom and we're going to go right through the whole—the whole section of that answer, okay? Mr. O'Rourke asked you a question starting—I'll read the question and you read the answer, okay?

A (Witness nods.)

Q Go through the whole thing this time.

MR. O'ROURKE: What line are you on?

MR. RUBIN: I'm sorry, page 117, line 21.

Q Question, "What did Jessica Fisch say to you regarding this treatment after she answered your question that by giving it IV it would work [209] more quickly or words to that effect?"

A "She said—the next thing she said was after I screamed—when I said—when I yelled 'that really hurts' what Jessica said is something to the effect of 'It's supposed to burn. This medicine burns. You need to hold still so you don't disturb the needle.' So I held still."

Q Question, "After answering your question about why she was going to give you medication IV she didn't say anything at all you remember until you remember yelling out or saying that something hurt and then she made a response to that remark that you made?"

A "Yes, she reassured me."

Q Question, "Now, when you say you felt something and yelled 'It hurts,' I have in my mind's eye of somebody yelling. Did you literally yell so that somebody standing out in the hallway would hear you? Or did you just in a voice say 'Jessica, that hurts' in a speaking voice, but not literally yelling? I'm trying to understand just what occurred."

Now, when that question was asked, did you attempt to say exactly in the same tone of voice?

[210] A (Witness nods.)

Q What did you say?

A "Ow, that really hurts."

Q Question, "Now, what you said was clearly in an elevated voice above a speaking voice." Answer?

A "Yes."

Q Did you scream?

A No.

Q You were trying to remember what happened in this situation at this time a year after or 13 months after it all happened?

A Yes.

Q Do you really remember at what point during this injection the burning or the pain started?

A No. I was in horrible pain and anything would be guesswork.

MR. RUBIN: Thank you.

Recross-Examination by Mr. O'Rourke

Q But when you answered those questions to the other examiner, you agreed you were under oath and you were recalling it as best you could?

A Yes.

Q The same as when you answered my

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MARCH 11, 2004

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[Testimony of Dr. Thomas Garvey III]

[85] should be used. Is that an instruction to physicians?

A. Certainly.

Q. The next sentence says, "When administering Phenergan intravenously, it is usually preferable to inject it through the tubing of an intravenous infusion set that is known to be functioning satisfactorily." What does that mean; is that an instruction to physicians?

MR. RUBIN: Objection, same basis. He's testifying about what an infusion set known to be functioning properly is a technical question.

THE COURT: I'll allow it. I think what we'd like to hear, Doctor, is what do these words mean, because they're not familiar to all of us.

A. Okay. First, let's—get to an infusion set. Usually an intravenous infusion set comes in a sterile sealed package and consists of tubing and connectors, and as well as it may have a cannula in it. It's usually an intravenous infusion set is usually used to connect a needle or a cannula in a vein, sometimes in [86] an artery, not in this case, in a vein to a source of intravenous fluid, either a pump or a hanging bag, so the set is a set of tubing. There are other ways to give IVs, as we all know, and it says here it says that it's usually preferable to inject this drug through the tubing of an intravenous infusion set that is known to be functioning satisfactorily. In this case you're in a vein, you get blood return, and you can put some saline in there and it flows freely, so pretty much you're in a vein, but it says "preferable," it doesn't say you always have to do, because, as you know, there are other situations you want to give a direct intravenous injection of Phenergan and other drugs, but it says that it's preferable. The downsides are time involved, lower concentrations achieved, and there are various other problems. Direct intravenous is quick, high concentration, with a bolus you get a shot of it.

Q. Okay. Then says "In the event that a patient complains of pain during intended intravenous injection of Phenergan Injection, the

* * *

[103] Tubex system is used for intravenous injection, the drug should be injected into a satisfactorily functioning intravenous set."

Q. And language close to this was put into the labeling for Phenergan?

A. Yes.

Q. So does this indicate that this language was provided by this Advisory Committee of experts?

A. Seems to be.

Q. Okay. While you were at FDA, were you aware of a program that the FDA initiated to change the formatting of labeling in the late '70s?

A. Yes.

Q. Can you describe that briefly to the jury?

A. Well, there were a lot of drugs on the market with labels that were very old and did not have uniform formats. Now, most of the drugs I dealt with, we already had draft guidelines for what the format should look like, and it was decided that the Agency should make happen that all of these old drugs with the old labels and funny formats, not necessarily funny formats, old formats should be redacted, in those cases the labels should be [104] redacted into the modern format, and they issued a so-called Federal Register notice instructing the firms that had such drugs to do so.

Q. Did Wyeth make a submission under this program for the Phenergan label?

A. Yes.

Q. And when was that submission made, if you know?

A. I think it was in '81.

Q. Okay. Let me go ahead and mark a document. I think you've got it, right?

A. The Federal Register notice requests having been made in '79 and amended. I—again, I think in '81, so the duration is not too unusual for this kind of thing.

MR. RUBIN: I'm sorry. I haven't seen this. It's eighteen pages.

THE COURT: All right. We've been at it for over an hour. We'll take a break, give you a minute to look it over, give everybody a chance to stretch.

(Court was in recess from 11:05 a.m. until 11:20 a.m.)

BY MR. HOFFMAN:

* * *

[128] well qualified. I think he was a full professor at the University of West Virginia in Morgantown which are disproportionately—not fair thing to say. Good medical center and is a balanced intelligent person.

Q. How long has he been at the FDA?

A. Oh, dear. I don't really know, fifteen, eighteen years, perhaps.

Q. And what's his current position at FDA?

A. He's the Director of the—of—of New Drugs.

Q. What does that mean?

A. He supervises all these new drug applications, neuro, pharmacologic, cardiac, renal, so forth and so on.

Q. The letter that we talked about, the February '97 letter, do you think that reflects an administrative error on the part of the FDA?

A. No.

Q. Okay. I want to mark, or, actually, I know it got marked into evidence. I was going to show you, this is defense Exhibit N. Is this Wyeth's response to the February '97 letter?

A. Yes.

Q. Okay. And does it provide the attached final

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[135] Q. I'm going to read you something from—I'll ask a preliminary question. When there would be meetings between drug companies and representatives of the FDA, was it common that the people from the FDA and the people from the drug company would decide that they would keep the minutes of the meetings secret so there would be no public access to those?

A. Well, there is certainly—excuse me. There's certain situations where they're secret. FDA is proprietary and meetings regarding a new drug application are generally considered, if you will, secret or confidential.

Q. Read—I'm going to read you a section of the Exhibit 17, and you remember who Dr. Clark was in this memorandum?

A. Yes.

Q. And that was a representative of the FDA?

A. Yes.

Q. Dr. Clark then commented that, "If we exchanged minutes, these would be subject to public availability under the FOI," Freedom of Information Act?

A. Yes.

* * *

[152] the vein, yeah, that's possible, sure.

Q. Let me try it again.

A. Sure, you want to try it again, we can try it again.

Q. You know the method by which this drug was administered?

A. In this case?

Q. Yes, the assume—let's assume the method we talked about was the method used in this case for purposes of this question. Would you like me to state that method again?

A. Yes.

Q. Take two Tubexes, each with 1 cc, you transfer those into a 3-cc syringe. This is a 3-cc syringe?

A. I'm familiar with them.

Q. You attach that 3-cc syringe to a butterfly infusion set. You're familiar with that device?

A. Yes, very much so.

Q. And then you administer the medication through this butterfly infusion set at a rate of 25 milligrams per minute, making sure that the fluid is flowing?

A. And your question is?

[153] Q. Is that consistent with the label?

A. I think it's consistent with the label, although I wonder why one would bother.

Q. You've answered my question. And it is foreseeable that a clinician would administer it the way it was administered to Diana Levine?

A. Now, you must remind me how it was administered to Diana Levine.

Q. Take 2 cc—two Tubexes, you transfer into that syringe, you attach it to the butterfly, and you push it slowly into the arm?

A. That wasn't my impression with respect to how it was delivered.

Q. It's not your understanding that 2 cc of Phenergan were transferred into a Tubex—into a 3-cc syringe, attached to a butterfly, and then administered into Diana Levine's arm?

A. My—

Q. You can answer that "yes" or "no." If it's not your understanding, that's fine.

A. That this was through a flowing system, no, I didn't remember knowing that was through a flowing system.

* * *

[168] system?

A. I'm not—is that the same question you asked me.

Q. Yes, it is.

A. I think my answer's the same.

Q. So you would not want to ensure that?

A. No, I would not want to preclude other methods of administration.

Q. So you would not want to ensure that it was done only through a free flowing established or piggyback system, correct?

A. Yes, that's correct.

MR. RUBIN: Can we have slide number on page 74.

MS. DeWOLFE: Begins, actually, on the bottom of page 73; is that correct?

Q. One second. Yes, it begins at the bottom of page 73, line 24. Question: "So given the high risk associated with extravasation or intra-arterial injection, I think what you're telling me is you would want, as a consultant, the label to ensure that the medication was piggybacked through an established IV?"

Answer: "The label unfortunately can't [169] ensure, that it can recommend."

Question: "The answer is, though, that you would want to write the label to instruct that; is that correct?"

Answer: "Yes."

A. Yeah, not exclusively sure.

Q. There's no question, Dr. Garvey.

A. Oh, I see.

Q. You are more than just a consultant; you also treat patients, as you said?

A. Well, I treat patients, yes.

Q. It was not a trick question. You are also a treating physician?

A. Yes.

Q. And you're concerned, obviously, about the welfare of your patient, right?

A. Patients, yes.

Q. And knowing what you now know, in a non-life-threatening situation, if the only benefit was to enhance

the speed of action, you would hesitate to use a butterfly system to administer this drug?

A. I think I would.

Q. One thing I noted that, when you testified earlier this morning, you said at some point

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[172] Q. Okay. You were asked if you would be hesitant to use a butterfly infusion set with Phenergan, do you recall that testimony?

A. Yes, just a moment.

Q. Does that mean that the use of that should be prohibited in all circumstances, use of a butterfly?

A. No. I think one needs to think a lot about it. There are some times when the only venous access is via small bore needle, for instance, with the butterfly sometimes you can't get in otherwise.

Q. You were asked about risk/benefit calculus. You're a gastroenterologist?

A. Yes.

Q. Do you treat patients who are extremely nauseous?

A. Nauseated, yes.

Q. Patients who are vomiting heavily?

A. Sure.

Q. What are some of the risks associated with heavy vomiting?

A. Dehydration, electrolyte imbalance, constipation, hypotension, arrhythmia.

Q. Were you done with your answer?

[173] A. I think I must have been, yes.

Q. And you know those risks as a gastroenterologist?

A. Even just as a regular old internist.

Q. Are there situations where a patient having that problem at risk for some of the serious consequences that you just described would need immediate relief?

A. Yes.

Q. So there is a class of patients for whom IV used through a butterfly is appropriate?

MR. RUBIN: Objection.

A. Yes, theoretically.

MR. RUBIN: Leading him through the way what he wants him to say, but it's a leading question.

THE COURT: I'll sustain the objection.

MR. HOFFMAN: I'll rephrase, Judge.

THE COURT: Thank you.

Q. Any patients that you can conceive of for use of a butterfly set would be appropriate?

A. Using a butterfly?

Q. Yes?

A. And direct injection?

[174] Q. Yes?

A. Somebody who has been vomiting to the point of severe hypobulimia, fluid depletion, veins are very tough to get into. You may be only able to get in with a butterfly. If they're vomiting, you want to get in right away, get in, give the drug. There are situations. I think the Agency was thinking about that.

Q. You were asked about a question and answer on page 128 of your deposition. I believe it was started on page 129, when you were asked, but I want you to go to two pages before, 127, line 25. I'll read you the questions, you read the answers, okay?

A. Okay.

Q. Question: "Well, I'm asking you to make an assumption. I don't know whether you have or not, let's just make an assumption—forget that. How many have you seen?"

Answer: "I think that among the 3500 as I think at last tally there was 32, I would have to recount, but I think it was 32."

And I'll stop here., Were you referring to adverse event reports here?

A. Yeah, I think so.

[175] Q. Next question: "How many of those involved some form of amputation?

Answer: "I haven't tallied them, I haven't had a chance to do this, but a substantial number."

So, when you told Mr. Rubin you meant a substantial proportion, you really needed to hear that question before to understand what you were saying?

A. Yes.

Q. In fairness?

A. Yes.

Q. All right. I have nothing further.

RECROSS-EXAMINATION BY MR. RUBIN:

Q. So of the 3200 or so adverse product events, adverse events that you reviewed, a substantial portion of or almost close to 32 of them were amputations?

A. No. I think that there were 32 amputations—32 intra-arterial injections or perhaps extravasations. Among them a substantial proportion involved amputation so some fraction of 32, not a small fraction.

MR. RUBIN: A substantial one. Thank you.

[176] MR. HOFFMAN: One question.

RE-REDIRECT EXAMINATION BY MR. HOFFMAN:

Q. I think you stated earlier you estimated it was approximately twenty.

A. That's what I remembered, yes.

MR. HOFFMAN: Okay, thank you.

THE COURT: Okay, Dr. Garvey. Thank you very much.

THE WITNESS: You're welcome very much.

MR. HOFFMAN: Your Honor, may we approach before the jury leaves?

THE COURT: Certainly.

MR. HOFFMAN: Over lunch Mr. O'Rourke and I talked and we've decided we're not going to call Nurse Patch.

THE COURT: Okay.

MR. HOFFMAN: And Dr. Greenblatt has told us he's going to get in his car at 6 a.m. and be here between 10 and 10:30. I'd like a little time with him. Would it be possible to start at, say, noon? I don't ex-

pect it will be long with him. Richard, I don't expect you're going to cross him.

THE COURT: Only one witness

* * *

MARCH 12, 2004

* * *

[Testimony of Dr. David J. Greenblatt]

[17] looked at, correct?

A. Yes.

Q. And I'm going to hand you a copy of the labeling that's already been marked. Take a look at it again. Do you have an opinion whether the labeling information provided concerning the risk of arterial injection of this product or inadvertent intra-arterial injection was accurate?

A. Yes, I do.

Q. Okay. Could you explain why?

A. I think the warnings are severe, given in multiple places in bold letters with the—the risks and the very bad consequences clearly outlined and warned against.

Q. Okay. Does the labeling provide enough instruction to physicians or physician's assistants for the safe use of the product?

A. Yes.

Q. Why do you believe that?

A. Well, it is known, for example, for this specific circumstance, that you have to have an intravenous access that is functioning properly for this drug to be given safely by the intravenous route of administration.

[18] It's very clear, and it's also clear what happened if that fails.

Q. Okay. What is "functioning properly" or "functioning satisfactorily," the verbiage in the label; what does that mean?

A. That means that the IV access is secure, that it's clearly in the vein, and that the fluid that is going in is clearly flowing into a vein and not into an artery and not outside the vein.

Q. And so we're clear, do you think that a butterfly infusion set is—can be a set that can be used with this medication?

A. Yes, it certainly can be.

Q. Okay, but, well, do precautions need to be taken to use that?

A. Absolutely.

Q. What kinds of precautions?

A. One, the administrator has to be very certain that the butterfly needle is—

MR. RUBIN: Objection. Can we approach?

THE COURT: Sure.

(At the bench):

MR. RUBIN: Again, he's not an

* * *

[26] knows how to read what secondary literature is out there, knows what the risks are.

THE COURT: I'll overrule the objection.

(In open court):

BY MR. HOFFMAN:

Q. Can I trouble you to read back the question. I've really forgotten it.

THE COURT REPORTER: "Let me ask you about risk/benefit now, specifically with respect to Phenergan. Do you think the IV use of Phenergan should be used"—

MR. HOFFMAN: Banned.

Q. Do you think the intravenous use of Phenergan should be banned, Doctor?

A. I don't think it should be banned.

Q. Why not?

A. This medication is given intravenously extensively throughout the United States and throughout the world. There are clinical situations in which to produce the needed relief of the patient that IV may be the preferable or the only way it may be administered. There are obvious risks to IV administration and they are extensively and [27] adequately warned against and, if the treating physician decides that the need to produce relief on that patient is urgent, then it's reasonable to give the drug IV to produce that relief if it's done properly.

Q. Why not give it as an intramuscular injection?

A. There are instances in which intramuscular injection is unreliable. Oftentimes an intramuscular injection, particularly in people who are overweight, may not actually get into a muscle but be injected into fat and be poorly absorbed. There may be cases in which somebody is seriously ill and has poor blood flow to a muscle, to the various muscle groups, because they may be dehydrated or they may have cardiac disease or something else is wrong with them, and even an injection that gets into a muscle may not be absorbed, so

there are circumstances in which an intramuscular injection is unreliable.

Q. Have you done studies about intramuscular injections?

A. Yes, we have.

Q. What about other therapies, aren't there

* * *

[32] in order to provide that kind of opinion?

A. I believe so.

Q. Let me ask you one last question?

A. Yes.

Q. Okay. How can it be that the benefits of getting a little quicker treatment of nausea or a little better treatment of nausea justify running the risk of the kind of terrible event that took place here?

A. Well, it's a judgment that is made by a treating physician who's treating a given patient and, if there is serious distress due to nausea and vomiting, if it won't stop, if the patient is miserable, if the patient is losing fluid and becoming dehydrated and very ill, then the physician in that urgent situation looks at what's available and, with knowing the risks of IV promethazine, would nonetheless make a judgment that the benefit to the patient is worthy of accepting that risk, and it's a clinical judgment when we're trying to, you know, when people are trying to take care of sick patients.

MR. HOFFMAN: I have no further questions. Thank you very much, Dr.

* * *

[35] done, it's not just me. There's a large research group, a number of people that I work with, so we do it.

Q. I understand that, but I think what would help us is your particular personal interest is in these areas, and then you work on a team to accomplish the results, right?

A. In part, yes.

Q. You're the chair of this Department?

A. Correct.

Q. And it has an endowment, it's an endowed chair?

A. In part, yes.

Q. In connection with your work as a clinical pharmacologist, I think you told Mr. Hoffman that some portion of the work or the studies that you do are funded by the drug companies that have an interest in the drugs that's being studied?

A. In some cases a small fraction overall has been supported by private sources.

Q. It is true that in the cases where you're working on the drugs that it's sometimes supported in part by the drug companies that have an interest in the medication that [36] you're testing?

A. Say that again. I didn't—

Q. I'm just asking whether you, in fact, get money from drug companies to assist in your research? And I know you said it's a small part, but that is true, right?

A. I don't get it personally, the University gets it, but there is support from pharmaceutical companies in some cases to assist in doing research.

Q. Okay. And, in fact, when you do research and complete your results, often you will publish those results in peer-review journal—medical journals?

A. Essentially all the time, yes.

Q. So, when the work is done, you publish the results for other professionals to share and learn from?

A. Correct.

Q. Actually, I did a little research about some of the studies that you've done. Lorazepam is a product made by whom?

A. By Wyeth.

Q. And in—I think first one I found was in 1977, you did a published a study with the [37] lead author called "Clinical pharmacokinetics of lorazepam"; do you remember that one?

A. Not specifically. Yes, that's correct.

Q. And Wyeth was acknowledged as one—one of the contributing fenders of that study?

A. Yes.

Q. I found another one, 1978, where you were the lead author of a study called "Analysis of lorazepam and its—some chemical component?

A. Yes, glucuronide metabolite.

Q. Right?

A. Right.

Q. And Wyeth helped or assisted in the funding of that study?

A. That's correct.

Q. I think I found another one in 1979, "Pharmacokinetics and bioavailability of oral lorazepam in humans or all different kinds of lorazepam in humans," '79, again you were the lead author in that one?

A. Yes, that's correct.

Q. That was a—Wyeth assisted in these?

A. All of these studies were principally funded by the National Institute of Health, but there was additional support beyond.

[38] Q. And this was a Wyeth product?

A. That's correct.

Q. There was another one I found more recently in 1998, I'm going to get this one wrong, "Comparative kinetics and dynamics on of zaleplon, zolpidem, and a placebo"?

A. Yes.

Q. Zolpidem is a Wyeth product, right?

A. Yes. We mentioned that in direct testimony.

Q. Okay, so that was 1998?

A. Yes.

Q. And that was assisted by a grant and aid from Wyeth-Ayerst Research in Radley, Pennsylvania?

A. That's right.

Q. I don't know if you mentioned this one, you might have, here's another one, "Kinetics and dynamics of lorazepam," you were the lead author in the Year 2000. Was that a similar study of Xanax or lorazepam?

A. This is Ativan, lorazepam, this was also mentioned in direct testimony.

Q. Performed in 2000?

A. Well, the study was actually done in the early—as discussed, it was done in the [39] earlier '90s but did not get published until 2000.

Q. And that got some grant funding from Wyeth, too?

A. That's correct.

Q. You got the appointment to the chair of this department in I think it's 1997?

A. '94.

Q. Okay. I saw a kind of a press release from Tufts which said "Tufts Professor Appointed to Pharmacology Chair," and appears to be referring to you. And this is called the Dr. Lasagna chair?

A. Yes.

Q. He's a well-reknown former clinical pharmacologist?

A. Yes.

Q. And this chair, professorship chair, was established with a million and a quarter dollars in private donations, including more than $650,000 from pharmaceutical companies?

A. Um, I'm not familiar with the source, but there is an endowed share, yes.

Q. And the pharmaceutical companies contribute generously and appropriately to the chair, to [40] the funding of this chair?

A. I believe that's the case, but I honestly don't know the details.

Q. In connection with your work, you also, as other doctors do, participate in seminars and meetings where you exchange information with other professionals on relevant topics?

A. Yes.

Q. Okay, and you are a member or are you a member of the American College of Clinical Pharmacology?

A. I am.

Q. I have a copy of a program from September 2002, it looks like it was a kind of some educational work that was done in connection with the annual business meeting. Do you happen to remember that in 2002?

A. If you let me look at it, maybe I'll remember.

Q. Sure. Take a look at page 13?

A. Yes.

Q. In that particular meeting you—it was actually a seminar. It appears to be on the relationship between some form of legal liability and your profession, right?

[41] A. Well, my particular role was to talk about the role of institutional review boards and clinical research in general.

Q. Fair enough. But this teaching forum was supported, as is usually the case or often the case, by educational grants by various drug companies, including Wyeth?

A. Could be. Yup.

Q. You work in a hospital setting?

A. Medical school setting.

Q. Do you work at the New England Medical Center downtown or do you work at Tufts?

A. Tufts University School of Medicine, which is across from New England Medical Center.

Q. That's in downtown Boston?

A. Yes.

Q. So it's a separate building but part of that New England Medical School's complex?

A. Two separate institutions. The medical school is part of Tufts University, which is actually the main University is in Medford, but Tufts New England Medical Center is a different corporate entity, and that's a hospital, and it's the main teaching hospital for Tufts University but it's—they're not [42] otherwise connected.

Q. Okay, so they've got the same first name but they're actually legally different?

A. Yes.

Q. You work at the Medical School?

A. My primary appointment is at the Medical School.

Q. But your clinical studies are done in the Hospital?

A. No, most are done in a clinical unit right in our own Medical School Department, but some clinical studies are done in the Hospital, in the general Clinical Research Center.

Q. So primarily you're working in a clinic, a clinic, if you will, which is part of your department at the Medical School?

A. Yes.

Q. Okay. And you don't treat migraine headaches?

A. No, I don't.

Q. And you don't prescribe antinausea drugs?

A. Correct.

Q. And from 1974 to 1990 I think you told me that less than five percent or less of your time was actually in the clinical practice of [43] medicine?

A. Correct.

Q. Essentially since you graduated from—completed your residency and perhaps some fellowship training, you have been doing clinical research as your primary work?

A. Basic and clinical research that's correct.

Q. And those five percent of the people that you did carry or see through 1990 were actually people who had been in a high blood pressure study; that was, while you were a resident, you kind of followed them along, or did I get that wrong?

A. No, they weren't in a study. As part of my fellowship training, we did outpatient clinic duty and, because my mentor treated hypertension, most of the patients that I acquired had primary disorder of high blood pressure, and I continued to follow them after training up until about 1990.

Q. Okay, and that was about five percent of your time?

A. No more than five percent.

Q. Since 1990, you have not had any clinical practice at all?

* * *

[45] or are healthy before they participate?

A. Most are, but not entirely. We do a lot of research in AIDS and HIV medications and those—most of those people are infected with HIV. Some are also normal volunteers, and there are studies like that that involve patients, but we don't treat the patients, themselves, they're participants in the studies.

Q. Since—I think you told Mr. Hoffman, since your training, you have no experience with Phenergan?

A. That's correct.

Q. Or any other antinausea drug to treat migraines?

A. I have not treated migraine.

Q. And you didn't undertake any independent research on the safety of Phenergan for IV use; you're relying on the warnings here, primarily?

A. What do you mean by "independent research"? I didn't do any studies.

Q. All right. You didn't talk to anybody at the FDA?

A. No.

[46] Q. Did you talk to anybody at Wyeth who has any role with this drug?

A. No.

Q. And I asked you what your general knowledge of Phenergan was, what your knowledge of Phenergan was, and it's true that you only had a general knowledge of its properties as a psychotropic drug?

A. Yes, I know that it's a thiephyazine, it has antihistaminic properties, which probably was why it's an antinausea drug. It does interact with the dopamine receptor which is an additional method by which it has antihistaminics properties, but it's not strong enough to be used, for example, with schizophrenia, for example, or psychosis.

Q. So you didn't talk to anybody at Wyeth about the drug. Did you, in fact, when I talked to you in November of 2002, you didn't even know whether it was used at your hospital?

A. Correct. I still don't.

Q. You don't know, then, clearly, if it is used at the hospital next door, how it's administered in the Emergency Department?

A. I don't know whether it's used at all or

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[49] A. Well, you still have to have access to the vein, so the needle insertion into the vein is what determines where it is. The infusion set is simply the—the means of administering the fluid into the vein by means of whatever needle you use.

Q. In fact, when you and I have talked, you—you thought that the warnings already required a free-flowing IV system, right?

A. I believe the warnings require a properly-functioning IV, which can—which does include free-flowing. It doesn't necessarily mean a hanging IV. A butterfly tube connected to a syringe could be functioning properly, as well.

Q. Could you open to page 46?

A. Um-hum.

Q. And actually line 23. I'm going over to line 2 on page 47.

A. Yes.

Q. And there's a question I asked you?

A. Um-hum.

Q. "So it's your opinion that the instructions do say it's preferable to put it through a free-flowing IV?" And your answer was:

* * *

[77] because they knew it was unsafe. They should have pulled their drug the way Pfizer pulled theirs from intravenous use. At a minimum, they should have required that you use a free-flowing IV. You've heard the discussion about how that free-flowing IV, that tube, and you guys can play with this in the jury room, or not, when you set that up and you let that saline run into the vein for a few minutes, you're going to know you're in the vein, it's got that soft catheter, you saw that, that bends. It's not going to migrate out of the vein. You use that, you know that you're not in an artery, because the back pressure of the artery is ten times the venous pressure and it stops the flow. Everybody said—except Dr. Garvey who I'll talk about in a minute, everybody said that, if it gets under the skin, it forms a little bubble, stops the flow, so you know, if you use that system, it's not a hundred-percent safe but it sure is a lot safer, and Wyeth knew it, too. And Dr. Greenblatt knew it, because he thought it was already in there.

I want to talk about the FDA. The [78] FDA this, the FDA that. Thank God we don't rely on the FDA to rely on this drug and make the safe decision. You will make the decision.

Dr. Garvey gets 750 an hour. I figured out, after he left Washington, worked 'til nine o'clock, started next morning, fifteen hours, he made probably between ten to fifteen thousand bucks to come up, 750 an hour.

Dr. Greenblatt is a prominent scientist. I'll talk about his opinion in a second. He gets two hundred dollars an hour. What are they paying Dr. Green—Dr. Garvey for? I'll tell you what they're paying him for. He came in here and said to you, I couldn't believe it, he

said, Oh, once Wyeth had that warning there, this one here, they couldn't change it without FDA approval. He said that you can't change it without FDA approval. I said, Really? You mean they can't change it to a free-flowing IV? He said, No, can't do it, gotta get prior approval, and he cited some old federal regulation.

* * *

[81] updated warning on inadvertent intra-arterial injection and perivascular extravasation, that's the leakage, becomes available to doctors and nurses since misinjection may cause severe tissue injury, and we believe the use of the updated warning is of critical importance for the safe use of Phenergan injection.

They never made the change. They could have, they didn't, and for some reason in 1998, why, the FDA says use the old warning. The FDA doesn't make the decision, you do. Wyeth was negligent, they were remiss, and their behavior, conduct, is unexplainable and inexcusable. They're certainly not justified.

Where's the witness? Look at the chair. Where's the witness from Wyeth that says, Well, let me explain to you, ladies and gentlemen, why we didn't change it, why we thought—you know, why we didn't initiate this. Let someone come in here besides Dr. Garvey and tell you, We didn't change this instruction or we thought the existing instruction was better, nobody. The FDA

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[83] don't say that with the 25. If this can do the damage that it did, we can assume and it seems to be the evidence that the 50 is too dangerous because, if it gets into your artery or leaks around or invades your artery, you're in trouble. But the evidence is the 25 will do exactly the same thing.

Dr. Green talked about the adverse events reporting the 25 dosage did exactly the same thing, so what are they doing? Where's the witness that will explain to you why they say don't use that 50-milligram dose intravenously, but it's okay -- I get a little choked up—it's okay to use the 25. Nobody comes up here. The reality is, neither one of them is safe for intravenous use with a butterfly, neither one of them. For thirty years they have known that and continued to market. You know, one thing that was interesting was they send their sales people up here to market their drugs, Marty Fitzgerald, to go by The Health Center a couple times a month, and they market their drugs, they sell the drugs. They're called detail men in the trade, and they hand out

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[Jury Instructions]

[145] THE COURT: All right, it's now my job to give you the Court's instructions regarding the law to apply in your deliberations. You'll get—you don't have to memorize, it you'll get a copy of the charge, each one of you, downstairs, so don't feel this is the only time you'll get to look at it, okay.

Ladies and gentlemen of the jury, now that you've heard all of the evidence and the arguments of counsel, it becomes my duty to give you the instructions of the Court concerning the law which governs this case. It is your duty as jurors to follow the law as I state it to you and to apply that law to the facts as you find them from the evidence presented in court. You're not to single out one instruction alone as stating the law. You should consider the instructions as a whole. Nor are you to be concerned with the wisdom of any rule of law stated by me. Regardless of any opinion you may have as to what the law is or ought to be, it would be a violation of your

sworn duty to base a verdict upon any view of the law other than [146] that given in the instructions of the Court. Similarly, it would be a violation of your sworn duty as judges of the facts to base a verdict upon anything other than the evidence presented during the trial.

Your job is to decide the facts based on what you heard and saw during the trial. This includes the testimony of the witnesses and the exhibits admitted by me. You will be given the exhibits in the jury room. In deciding the facts, you must not be swayed by sympathy or prejudice towards either side.

My job is to give you the law. After you decide the facts, you need to apply the law that I give you, even if you do not agree with it. Remember that statements, objections, or arguments made by the lawyers are not evidence in the case. The lawyers' job is to point out those things that are most significant or most helpful to their side of the case, which you otherwise might not have noticed. You should also not assume from any statements that I may have made that I have any opinion about how you should [147] decide this case.

In considering the evidence, you are not limited to the bare statements of the witnesses. You may draw reasonable conclusions from the testimony and exhibits based on common sense and experience. However, you may not guess about what testimony or exhibits that were not admitted into evidence might have shown.

Credibility of witnesses. You must consider all of the evidence. This does not mean that you must believe all of the evidence. You are the sole judges of the reliability of each witness and the weight that each witness's testimony should be given. In evaluating the testimony of witnesses, you should consider whether they have any interest in the outcome of the case, their

demeanor while testifying, their candor, any bias they might have, and the extent to which other believable evidence in the case fits with their testimony. You should also consider their ability or opportunity to see or hear the facts about which they have testified, and whether they [148] remember these facts accurately. You may believe as much or as little of each witness's testimony as you think appropriate. Keep in mind that people sometimes forget things or make mistakes in their testimony. You must decide whether an error is innocent or minor or something more which affects the rest of their testimony.

Expert Witnesses. Some witnesses testify for the purpose of giving an opinion on the basis of special knowledge. In this case both sides called expert witnesses. These include doctors and persons with other scientific expertise. First, you should evaluate an expert witness in the same way you would any other. Then you should evaluate whether the opinion is well grounded in approved facts and supported by the witness's learning and experience.

Burden of proof. Ms. Levine must prove each element of her claims by a preponderance of the evidence. A preponderance of the evidence means the more convincing evidence. It does not mean the most witnesses. It is a matter of quality, [149] not quantity. If the evidence tends to be equally balanced, the party who has the burden of proof cannot proceed on his or her claim. Think of the test as the 51 percent rule, in light of the evidence and the law, do you believe that the claim is more likely true than not.

Now, the Claims. Plaintiff, Diana Levine, makes two claims against Wyeth. These are that Wyeth acted negligently in failing to provide adequate instructions

to the physicians or other medical professionals about the use of the drug Phenergan and that Wyeth is strictly liable for failing to warn of the risks of the drug Phenergan. Wyeth denies both these claims and states that the warnings and instructions were adequate and they were not the cause of Ms. Levine's injury. You should consider each of these claims separately.

FDA Regulation. Before I instruct you about the elements of the Plaintiffs claim, I will say a word about the FDA. You may consider evidence of compliance by Wyeth with FDA requirements in obtaining approval **[150]** for the Phenergan warning. Compliance with the FDA requirements, by itself, does not establish that the warning was adequate for purposes of this case. You must decide whether the instructions and warning were adequate based upon all of the evidence presented in this trial including evidence about the FDA process. The FDA regulations, 21 CFR section 314.70, permit a drug manufacturer to change a product label to add or strengthen a warning about its product without prior FDA approval so long as it later submits the revised warning for review and approval.

Now, the Claims: Negligence. A claim of negligence has three essential elements: A duty of care, breach or violation of that duty, damage or injury caused by the breach of duty. I'll discuss each one of these with you in the context of this case.

Duty of care: The manufacturer of a product such as Wyeth has a duty to take reasonable steps to notify users of the product, in this case the medical community, **[151]** of the risks and dangers of the product and to provide adequate instructions about how to use the product safely. This standard of conduct of reasonable care does not require that useful drugs with dangerous

potential be removed from the market; instead, the law requires that Wyeth exercise reasonable care to warn or protect against the risks. The standard is what would a reasonable manufacturer have done under similar circumstances to provide warning and instruction about the risks of the product.

Warnings for prescription drugs are intended for the physician and staff whose duty it is to balance the risks against the benefits of various drugs and treatment and to supervise their effects. You may consider the facts you have heard about in the course of this trial, including the seriousness of the risks to patients, the likelihood or incidence of injury, and the content of warning and advice provided by Wyeth.

Duty to warn: First you have to determine the nature and extent of Wyeth's duty to warn and advise about a—duty to [152] warn and advise about the risks of injury the patients—to patients presented by Phenergan. You must decide the extent to which Wyeth should have warned and advised of the risks and injuries which could result from an injection of Phenergan of the type conducted in this case. The manufacturer's duty is to warn of all potential dangers in its prescription drugs that it knew or in the exercise of reasonable care should have known to exist. It's for you to decide the nature and scope of the warning required.

Violation of duty: After you've determined the nature of the warning required, you must consider whether the information presented by Wyeth to physicians at the time Ms. Levine received the drug complied with this duty or fell short of compliance. In other words, you must decide what a reasonable drug manufacturer should do to inform physicians about the risks and potential harm presented by Phenergan when

administered by injection, and then you must decide whether Wyeth's action met the standard or not. The warning must reasonably [153] advise of the risks and provide adequate instructions to the physician or other medical professional for its safe use.

Causation. If you determine that Wyeth breached its duty to warn, you must determine whether any breach of the duty to warn caused Ms. Levine's injuries. You should consider whether an adequate warning or instruction would have been read and followed, and whether reading and following an adequate warning would have prevented Ms. Levine's injuries. Bear in mind on the issue of causation that an event may have several causes. Some of these causes are very direct and obvious, others are more remote. Your job in determining legal cause is to ask yourselves this question: Did the Defendant's negligence lead to the Plaintiff's injury in an understandable chain of cause and effect. The law does not require that the negligent act be the sole cause of the injury. Several factors may combine to cause an injury. The Plaintiff is required to show that an act of negligence by the Defendant was a substantial factor in [154] causing her injury.

Intervening event. Wyeth claims that the action of Ms. Fisch in continuing to administer Phenergan to Ms. Levine after Ms. Levine complained of pain was an intervening event which breaks any causal connection between the product warnings and instructions and Ms. Levine's injury. On this issue, Wyeth has the burden of proof by a preponderance of the evidence, which means more likely than not. In order for an event to break the chain of causation between an initial act of negligence and the injury, the intervening event must be unforeseeable by Wyeth. The intervening event must also be, itself, a cause of the injury. The chain of causation is

broken if you find that Wyeth could not anticipate that a physician's assistant in Ms. Fisch's position would complete the injection after the complaint of pain and that stopping the injection when Ms. Levine complained of pain would have prevented her injury. You must decide if Wyeth has met its burden of proof on intervening cause. If you find that it has, [155] then you should find that Wyeth's conduct, even if negligent, was not a cause of injury for purposes of this lawsuit. If you decide that Wyeth was negligent and that this negligence was a cause of Ms. Levine's injury, you should find for Ms. Levine on this issue. If you find that Wyeth was not negligent and that any cause was not a cause of or that an intervening event broke the chain of causation, you should find for Wyeth on this issue. In either event, you should now consider the claim of strict liability.

Now I'm going to get a glass of water.

Strict Liability. Failure to Warn: A manufacturer of a product such as Phenergan is responsible for harm to a person caused by a defective product that reaches a user without undergoing substantial change. In this case there is no dispute that Ms. Levine was injected with the drug Phenergan which was manufactured by Wyeth and that the product was not changed between the date it was manufactured and the time of injection. The parties disagree over whether the drug [156] was defective as a result of inadequate warning.

In this case the term "defective" means unreasonably dangerous. A prescription drug is unreasonably dangerous due to inadequate warnings or instructions if reasonable instructions or warnings regarding foreseeable risks of harm are not provided to the physician and other medical professionals who are in a position to reduce the risks of harm. Just as in the neg-

ligence claim, the disputed issue is whether the warning and instructions provided by Wyeth were adequate concerning the risks of injection of Phenergan. The warning must reasonably advise of the risks and provide adequate instructions to the medical professionals for its safe use. This is the critical factual issue which you must decide on the basis of the evidence of the risks and benefits of intravenous administration and the potential for injury to patients.

Causation. Finally, if you decide that the warning or instruction was inadequate, you must decide whether this [157] inadequacy was a cause of the injury. You should consider whether an adequate warning or instruction would have been read and followed and whether reading and following an adequate warning or instruction would have prevented Ms. Levine's injuries. As in the case of the negligence claim, you should bear in mind that the law does not require that an inadequate warning or instruction be the sole cause of the injury. Several factors may combine to cause the injury. The Plaintiff is required to show that an inadequate warning or instruction was a substantial factor in causing her injury.

The defense of intervening event also applies to the strict liability claim. Wyeth has the burden of proof on this issue by a preponderance of the evidence. If you find that Wyeth has shown that the action of Ms. Fisch, in continuing to administer Phenergan to Ms. Levine after her complaint of pain was not foreseeable by Wyeth, and that stopping the injection when Ms. Levine complained of pain would have prevented her injury, then you should find for Wyeth on the [158] issue of causation. You should reach a decision on your verdict form on both the issues of negligence and strict liability.

Damages. If you decide in favor of the Defendant on both counts of negligence and strict liability, you should enter a verdict for the Defendant on the verdict form and cease your deliberations. You will not consider these instructions about damages. But, if you decide in favor of Ms. Levine on either the claim of negligence or the claim of strict liability or on both claims, you shall award Ms. Levine an amount of money that you believe will put her as nearly as possible in the position she would have occupied if the injury to her right arm had not happened. Here are some further instructions to help you do that. Ms. Levine has the burden of proof by an preponderance of the evidence on each element of her claim for damages.

Personal injury damages. Ms. Levine is entitled to compensation for any bodily injury and any pain and suffering, disability, disfigurement, mental anguish, [159] and loss of enjoyment of life experienced in the past or probably to be experienced by her in the future. You should award monetary compensation for these damages for any harm you find caused by the injury to her right arm and related conditions. There is no particular formula to calculate this compensation. You should make sure that any amount awarded to Ms. Levine is fair, just, and reasonable, in light of the evidence you have heard.

Medical expenses, personal care, and equipment: Ms. Levine is entitled to compensation for the cost of medical treatment, personal care treatment, and modifications of her home, reasonably necessary in the past or that will probably be necessary in the future because of the injury to her arm.

Lost earnings and earning capacity. Ms. Levine is entitled to compensation for any lost earnings in the past and any probable loss of ability to earning in the future

because of her injury to her right arm. When considering Ms. Levine's future **[160]** earnings, you should consider her expected working lifetime. Reasonable, not speculative damages must be supported by the evidence. You must not award damages based upon speculation.

Income taxes. If you find for Ms. Levine, you must not consider any effect of federal or state income tax in deciding the award.

Interest. The Court will resolve the issue of interest on any damages following your verdict. You should not add any additional amount of your award for interest.

Recovery from any other source. In this case you heard evidence that there was a claim against the physician and The Health Center. This evidence was admitted for the limited issue of credibility. I discussed this issue with you at the time. I instruct you now that you should not speculate or consider the effect of any other recovery or payment from another source in considering the issue of damages. If you award damages, the amount should be for the full amount of **[161]** Ms. Levine's loss as you determine it.

Foreperson. The Court appoints Barbara Butler as your foreperson. She will be responsible for guiding your deliberations and making sure that everyone is able to participate fully. Your verdict must be unanimous. A verdict form will be provided for your use, and you will also receive the exhibits in a couple of minutes.

And that concludes my instructions.

Counsel want to approach?

(At the bench):

MS. DeWOLFE: Your strict liability portion of the charge, you changed in one of the instructions. I asked

that you did that in negligence. I'm assuming the jury will infer there was some distinction when you say "warnings" and "warnings and instructions." That's a bit of a hassle, but I think it's important. No. 2, we would object to your decision not to give the so-called "Read and Heed Presumption," Bridport V. Sterling case, and I continue to object to the intervening negligence charge that's been given here and, instead, would request the instruction I [162] drafted on causation. I think that does it. Thank you very much.

MR. KEYES: The objections, the first is on the failure to charge comparative fault between The Health Center. We filed a request to charge and a trial memo on that issue and asked for the jury to determine a comparative negligence between the two. Both have been sued. On intervening cause, we feel the Patent v. Sawyer case is an exception to the rule, that there's no intervening cause when we have a duty to anticipate the negligence and that is exception when the intervening actor becomes aware of the risk and knowingly proceeds. We submitted a supplemental charge on intervening cause this morning and object to the Court's failure to include that, and, third, is an objection to the Court's failure to have a charge on reduction to present value for future losses, both generally and particular to the closing argument which was asking for an hourly computation of future losses.

THE COURT: Okay. Good enough. [163] Your objections are noted. Thank you.

MS. DeWOLFE: Thank you, Judge.

THE COURT: Okay.

(In open court):

THE COURT: Okay, you can retire to your jury room and start your deliberations. Before you go, let me just say this, that your work now is the most important thing that this court has going, so take all the time you need, and we'll stay late for you, as long as, Ms. Butler, as everybody is working in a productive, helpful way, we'll stay 'til you tell us okay, and the State will buy you some dinner.

(The jurors left the courtroom at 3:43 p.m)

(In open court at 5:06 p.m.):

THE COURT: All right, we're back on the record; and, Mr. O'Rourke, did you want to offer an exhibit?

MR. O'ROURKE: Yes, Court's Exhibit JJ, which is the Covenant, your Honor. We'd like to offer that.

THE COURT: Is it confidential in some way?

* * *

[Jury Verdict]

[166] amount up to that number, which we believe to be around $220,000 pre-judgment interest, statutory rate will be computed upon that amount. We're specifically waiving any pre-judgment interest on past lost wages because of a strategic decision about how we wanted the verdict form designed.

MR. O'ROURKE: Pre-judgment will be worked out between Kerry and myself.

THE COURT: On the basis of the dates the charges were incurred?

MS. DeWOLFE: Correct.

(Court was in recess from 5:11 p.m. until 7:52 p.m.)

THE COURT OFFICER: Members of the jury, has the jury reached a verdict?

THE FOREPERSON: Yes, we have.

(The court officer approached the bench.)

THE COURT OFFICER: In the case entitled Diana Levine vs. American Home Products, Inc., now Wyeth, this is the verdict of the jury.

Question 1: Do you find that Wyeth was negligent in this case?

[167] Answer: Yes.

Question 2: Was the negligence of Wyeth a cause of Diana Levine's injuries?

Answer: Yes.

Question 3: Did an intervening cause break the causal connection between Wyeth's negligence and Diana Levine's injuries?

Answer: No.

Question 4: Was the product Phenergan defective when administered to Diana Levine as a result of inadequate warnings and instructions?

Answer: Yes.

Question 5: Were the inadequate warnings or instructions a cause of Ms. Levine's injuries?

Answer: Yes.

Question 6: Did an intervening cause break the causal connection between a defect in the product Phenergan and Ms. Levine's injuries?

Answer: No.

Question 7: Please state the amounts of damages you award for the following elements of Ms. Levine's claim:

Economic losses and costs, medical [168] care, medical expenses, personal care, and equipment costs, lost earnings, and earnings capacity: 2.4 million dollars.

Non-economic losses, personal injury damages: Five million dollars.

Do you wish the jury polled?

Do you wish the jury polled?

MR. O'ROURKE: No, your Honor.

THE COURT: And, Ms. Butler, is this the verdict of the jury?

THE FOREPERSON: Yes, sir.

THE COURT: Thank you all for your service. I think you've all—

Is there anything to take up with the jury from either of you?

MR. O'ROURKE: I don't think there is, your Honor.

MR. RUBIN: No. In fact, thank you, your Honor.

THE COURT: I think you can all go. I thank you very much for your service in this case.

(The jurors left the courtroom.)

THE COURT: Okay, have a seat, please.

* * *

STATE OF VERMONT
COUNTY OF WASHINGTON, SS.

DIANA LEVINE

v.

Washington Superior Court
Docket No.: 670-12-01

AMERICAN HOME PRODUCTS, INC.
(Now Wyeth).

JURY INSTRUCTIONS

Ladies and gentlemen of the jury:

Now that you have heard all of the evidence, and the arguments of counsel, it becomes my duty to give you the instructions of the court concerning the law which governs this case.

* * *

CLAIMS

Plaintiff Diana Levine makes two claims against Wyeth: these are that Wyeth acted *negligently* in providing information to physicians and medical personnel about the risks fo the drug Phenergan and that Wyeth is *strictly liable* for failing to warn of the risks of the drug Phenergan. Wyeth denies both of these claims and states that the warnings and instructions were adequate and that they were not the cause of Ms. Levine's injury. You should consider each of these claims separately.

FDA Regulation

Before I instruct you about the elements of the plaintiff's claim, I will say a word about the FDA.

You may consider evidence of compliance by Wyeth with FDA requirements in obtaining approval for the Phenergan warning. Compliance with the FDA re-

quirements by itself does not establish that the warnings was adequate for purposes of this case. You must decide whether the instructions and warnings were adequate based upon all of the evidence presented in this trial including evidence about the FDA process.

The FDA regulations, 21 C.F.R. S 314.70, permit a drug manufacturer to change a product label to add or strengthen a warning about its product without prior FDA approval so long as it later submits the revised warning for review and approval.

Negligence

A claim of negligence has three essential elements: a duty of care; breach or violation of that duty; damage or injury caused by the breach of duty. I will discuss each one of these with you in the context of this case.

Duty of Care

The manufacturer of a product such as Wyeth has a duty to take reasonable steps to notify users of the product—in this case the medical community—of the risks and dangers of the product and to provide adequate instructions about how to use the product safely. This standard of conduct of reasonable care does not require that useful drugs with dangerous potential be removed from the market. Instead, the law requires that Wyeth exercise reasonable care to warn or protect against the risks.

The standard is what would a reasonable manufacturer have done under similar circumstances to provide warning and instruction about the risks of the product. Warnings for prescription drugs are intended for the physician and his staff whose duty it is to balance the risks against the benefits of various drugs and treatments and to prescribe them and supervise their effects. You may consider the factors you have heard

about in the course of this trial including the seriousness of the risk to patients, the likelihood or incidence of injury, and the content of the warning and advice provided by Wyeth.

Duty to Warn

First, you have to determine the nature and extent of Wyeth's duty to warn and advise about the risks of injury to patients presented by Phenergan. You must decide the extent to which Wyeth should have warned and advised of the risk and injuries which could result from an injection of Phenergan of the type conducted in this case. The manufacturer's duty is to warn of all potential dangers in its prescription drugs that it knew, or in the exercise of reasonable care, should have known to exist. It is for you to decide the nature and scope of the warning required.

Violation of Duty

After you have determined the nature of the warning required, you must consider whether the information presented by Wyeth to physicians at the time Ms. Levine received the drug complied with this duty or fell short of compliance. In other words, you must decide what a reasonable drug manufacturer should do to inform physicians about the risks and potential harm presented by Phenergan when administered by injection and then you must decide whether Wyeth's actions met this standard or not. The warning must reasonably advise of the risks and provide adequate instructions to the physician or other medical professional for its safe use.

Causation

If you determine that Wyeth breached its duty to warn, you must determine whether any breach of the duty to warn caused Ms. Levine's injuries. You should con-

sider whether an adequate warning or instruction would have been read and followed and whether reading and following an adequate warning would have prevented Ms. Levine's injuries.

Bear in mind on the issue of causation that an event may have several causes. Some of these causes are very direct and obvious. Others are more remote. Your job in determining "legal" cause is to ask yourselves this question: did the defendant's negligence lead to the plaintiff's injury in an understandable chain of cause and effect?

The law does not require that the negligent act be the sole cause of the injury. Several factors may combine to cause an injury. The plaintiff is required to show that an act of negligence by the defendant was a substantial factor in causing her injury.

Intervening Event

Wyeth claims that the action of Ms. Fisch in continuing to administer Phrenegan to Ms. Levine after Ms. Levine complained of pain was an "intervening event" which breaks any causal connection between the product warnings and instructions and Ms. Levine's injury. On this issue, Wyeth has the burden of proof by a preponderance of the evidence which means more likely than not.

In order for an event to break the chain of causation between an initial act of negligence and the injury, the intervening event must be unforeseeable by Wyeth. The intervening event must also be itself a cause of the injury. The chain of causation is broken if you find that Wyeth could not anticipate that a physician's assistant in Ms. Fisch's position would complete the injection after a complaint of pain and that stopping the injection when Ms. Levine complained of pain would have prevented her injury.

You must decide if Wyeth has met its burden of proof on the issue of intervening cause. If you find that it has, then you should find that Wyeth's conduct, even if negligent, was not a cause of the injury for purposes of this lawsuit.

If you decide that Wyeth was negligent and that this negligence was a cause of Ms. Levine's injury, you should find for Ms. Levine on this issue. If you decided that Wyeth was not negligent, that any negligence was not a cause of Ms. Levine's injury or that an intervening event broke the chain of causation, you should find for Wyeth on this issue. In either event, you should now consider the claim of strict liability.

Strict Liability—Failure to Warn

A manufacturer of a product such as Phenergan is responsible for harm to a person caused by a defective product that reaches a user without undergoing substantial change. In this case, there is no dispute that Ms. Levine was injected with the drug Phenergan which was manufactured by Wyeth and that the product was not changed between the date it was manufactured and the time of injection. The parties disagree over whether the drug was defective as a result of inadequate warning.

In this case, the term "defective" means unreasonably dangerous. A prescription drug is unreasonably dangerous due to inadequate warnings or instructions if reasonable instructions or warnings regarding forseeable risks of harm are not provided to the physician and other medical professionals who are in a position to reduce the risks of harm.

Just as in the negligence claim, the disputed issue is whether the warning and instructions provided by Wyeth were adequate concerning the risks of injection

of Phrenagen. The warning must reasonably advise of the risks and provide adequate instructions to the medical professionals for its safe use. This is the critical factual issue which you must decide on the basis of the evidence of the risks and benefits of intravenous administration and the potential for injury to patients.

Causation

Finally, if you decide that the warning or instruction was inadequate, you must decide whether this inadequacy was a cause of the injury. You should consider whether an adequate warning or instruction would have been read and followed and whether reading and following an adequate warning or instruction would have prevented Ms. Levine's injuries. As in the case of the negligence claim, you should bear in mind that the law does not require that an inadequate warning or instruction be the sole cause of the injury. Several factors may combine to cause an injury. The plaintiff is required to show that an inadequate warning or instruction was a substantial factor in causing her injury.

The defense of "intervening event" also applies to the strict liability claim. Wyeth has the burden on proof on this issue by a preponderance of the evidence. If you find that Wyeth has shown that the action of Ms. Fisch in continuing to administer Phrenegan to Ms. Levine after her complaint of plain was not foreseeable by Wyeth and that stopping the injection when Ms. Levine complained of pain would have prevented her injury, then you should find for Wyeth on the issue of causation.

You should reach a decision on your verdict form on both the issues of negligence and strict liability.

* * *

STATE OF VERMONT
COUNTY OF WASHINGTON, SS.

DIANA LEVINE

v.

Washington Superior Court
Docket No.: 670-12-01

AMERICAN HOME PRODUCTS, INC.
(Now WYETH).

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(initials)
MAR 12 2004
SUPERIOR COURT
WASHINGTON COUNTY

JURY VERDICT

I.. Negligence

1. Do you find that Wyeth was negligent in this case?

Yes √

No_____

If your answer is Yes, please continue to question 2. If your answer is No, please go directly to question 4.

2. Was the negligence of Wyeth a cause of Diane Levine's injuries?

Yes √

No_____

If your answer is Yes, please continue to question 3. If your answer is No, please go directly to question 4.

3. Did an "intervening cause" break the causal connection between Wyeth's negligence and Diana Levine's injuries?

Yes_____

No___√___

Now, go to question 4.

II. Strict Liability

4. Was the product Phenergan defective when administered to Diana Levine as a result of inadequate warning and instructions?

Yes___√___

No_____

If your answer is Yes, please continue to question 5. If your answer is No, please go to the instructions after question 6.

5. Were the inadequate warnings or instructions a cause of Ms. Levine's injuries?

Yes___√___

No_____

If your answer is Yes, please continue to question 6. If your answer is No, please go to the instructions after question 6.

6. Did an "intervening cause" break the causal connection between a defect in the product Phenergan and Ms. Levine's injuries?

Yes___√___ inadvertent checkmark (initials)

No √

Instructions

If you have answered Yes to questions 1 and 2 (and No to question 3), OR if you have answered Yes to questions 4 and 5 (and No to question 6), you should consider the issue of Damages.

Please state the amount of damages you award for the following elements of Ms. Levine's claim:

Economic losses and costs (Medical expenses, personal care and equipment costs, lost earnings and earning capacity	$ $2,400,000
Non-Economic losses (Personal injury damages)	$ $5,000,000

Dated: March 12, 2004

/s/
Foreperson

STATE OF VERMONT
WASHINGTON COUNTY, SS.

DIANA LEVINE	)	
	)	WASHINGTON SUPERIOR
v.	)	COURT
	)	DOCKET NO. 670-12-01 Wncv
WYETH	)	

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SUPERIOR COURT
WASHINGTON COUNTY

JUDGMENT

This matter was tried before a jury, Honorable Geoffrey W. Crawford presiding, which rendered its verdict for the plaintiff, Diana Levine, on March 12, 2004. Based upon the verdict, the amount of an earlier settlement, and the parties' agreement for $74,000 in pre-judgment interest, it is Ordered and Adjudged that the plaintiff, Diana Levine, recover from the defendant, Wyeth, the sum of $6,700,000, plus $74,000 pre-judgment interest, for total of $6,774,000.

Dated at Montpelier, Vermont this 17th day of March, 2004.

/s/
Honorable Geoffrey W. Crawford

Approved as to form:

/s/ by (initials) with permission
Allan R. Keyes Esq.

STATE OF VERMONT
COUNTY OF WASHINGTON, SS.

DIANA LEVINE,
Plaintiff

v.

Washington Superior Court
Docket No.: 670-12-01

AMERICAN HOME
PRODUCTS, INC.
(Now Wyeth),
Defendant.

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SUPERIOR COURT
WASHINGTON COUNTY

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DECISION ON MOTION FOR JUDGMENT UNDER V.R.C.P. 50

This is a motion for judgment under Rule 50 following entry of judgment in a product liability case. The motion was timely filed and follows an earlier motion for judgment on the same grounds submitted at the close of the evidence.

Factual Background

This case arises out of an incident on April 7, 2000, when plaintiff received an injection of the drug Phenergan from physician's assistant Jessica Fisch at the Health Center in Plainfield, Vermont. Phenergan is an anti-nausea medication manufactured and sold by de-

fendant. As a result of the injection, plaintiff developed gangrene in her right hand. She underwent an amputation of her right arm at the elbow. Plaintiff settled a separate claim against the Health Center and her physician prior to suit.

The parties tried this case from March 8–March 11, 2004. The jury verdict was for $7,400,000. The parties stipulated to adjustments for the prior settlement and pre-judgment interest. The Court entered judgment on March 17, 2004, for $6,774,000.

Standard of Review

The standard of review for a Rule 50 motion is whether "during a trial by jury a party has been fully heard on an issue and there is no legally sufficient evidentiary basis for a reasonable jury to find for that party on that issue." V.R.C.P. 50(a). If the basis for the jury's verdict is insufficient, "the court may determine the issue against that party." *Id.* The trial court may grant the motion against a party "with respect to a claim or defense that cannot under the controlling law be maintained or defeated without a favorable finding on that issue." *Id.*; see also *Brueckner v. Norwich University*, 169 Vt. 118, 122 (1999) ("[A] trial court considers the evidence in the light most favorable to the nonmoving party, excluding the effect of any modifying evidence.") (citation omitted).

I. Federal Preemption by FDA approval of Phenergan labeling

Plaintiff's claim against defendant is based on allegations that defendant failed to warn of the hazards of intravenous injection of Phenergan. At trial plaintiff introduced evidence that Phenergan should be administered by intra-muscular injection or through a free-

flowing IV bag. Plaintiff's witnesses testified that injection into the patient's vein through a "butterfly" infusion set was too dangerous and should have been strongly discouraged in the instructions for use—the "package insert" or label which accompanies the product when it is provided to a physician.

Defendant argues that the approval of the Phenergan label by the Food and Drug Administration preempts Vermont product liability law on the issue of labeling and provides a defense as a matter of law to a claim based on failure-to-warn.

Factual Record at Trial

At trial defendant received wide latitude to introduce evidence about its interaction with the FDA concerning the Phenergan label. The factual record relevant to the Rule 50 motion is as follows:

1. The corrosive nature of Phenergan can lead to catastrophic tissue damage if it enters a patient's arterial blood flow. As the arteries become smaller and more diffuse, the tiny vessels can be damaged by exposure to Phenergan. The patient suffers spasm of the arteries, inflammation, loss of blood flow due to clotting, gangrene, and, in some cases, the loss of a limb or other serious injury. Green, Tr. 212, 216. Once Phenergan enters the arterial flow, there is no reliable way to reverse the harmful effects of the medication on the tiny vessels distal (downstream) from the site of the injection. Green Tr. 213.

2. In this case, plaintiff received an injection of Phenergan through the use of a "butterfly" intravenous infusion set. The butterfly set consists of a needle which is placed in the patient's vein and held in place by two flexible tabs—the "butterfly." The infusion set creates

a fixed point of entry into the vein. Medication can then be injected through the infusion set into the patient's vein. Alternatively, the infusion set can be hooked up to a free-flowing IV bag. Medication such as Phenergan can be added to the IV solution and administered through the IV drip. Matthews, Tr. 85-100. Ms. Fisch injected 50 milligrams of Phenergan directly through the butterfly infusion set into plaintiff's arm over the course of several minutes. She did not use a free-flowing IV bag. Matthews, Tr. 89-93.

3. For reasons that remain unclear, the Phenergan entered plaintiff's arterial system, either because the needle in the infusion set entered an artery directly or because the drug leaked out of the vein and entered an artery through a process called extravasation. Green Tr. 211. As a result of the injection, plaintiff suffered catastrophic injury to her right arm.

4. One way to reduce the risk of inadvertent intra-arterial injection is to set up a free-flowing IV bag and introduce the drug into the IV solution. This is an alternative to injection through the infusion set into a patient's vein. Administration through a free-flowing IV bag reduces the risk of inadvertent arterial injection because the nurse or physician can be more certain that the needle has been placed in a vein. A solution dripping from an IV bag will not flow freely into an artery due to back pressure from the patient. Green Tr. 194-98, 208-14.

5. The FDA has approved the label for Phenergan since at least 1974. Defendant Ex. P.

6. Since at least 1976, both the FDA and defendant have recognized that injection of Phenergan into an artery is dangerous and can result in severe injury. Defendant Ex. R. By 1976, the Phenergan label contained

specific warnings about the hazard of intra-arterial injection. Defendant Ex. S.

7. The minutes of an FDA anesthesiology advisory committee meeting on 10/14/76 include discussion of the Phenergan label then in use. The committee considered a variety of concerns including the risk of intra-arterial injection. The committee recommended that an additional warning should be added: "If a Tubex system is used for intravenous injection, the drug should be injected into a satisfactorily functioning intravenous set." Ex. S.

8. In 1979, the FDA required extensive relabeling of pharmaceutical drugs, including Phenergan. The defendant gave some consideration to changing the warnings about intra-arterial injection to recommend use of an intravenous infusion set for administration of the drug. A 1981 proposed package insert contained the following language:

> When administering any irritant drug intravenously, it is usually preferable to inject it through the tubing of an intravenous infusion set that is known to be functioning satisfactorily.

Ex. T. Defendant submitted the same proposed language to the FDA on 5/3/88 in conjunction with other proposed changes to the Phenergan label. Ex. M. The proposed language was never used.

9. In a letter to defendant dated 2/21/97, an FDA official directed defendant to "retain verbiage in current label" with respect to the risk of inadvertent intra-arterial injection. No warning or instruction concerning the preferred use of an intravenous infusion set appeared in the defendant's label, including the label in

use when the dose of Phenergan involved in this case was sold.

10. The letter dated 2/21/97 identifies the "current label" as the version which defendant submitted to the FDA by letter on 8/6/96. The defendant was unable to obtain a copy of the 8/6/96 letter until after the completion of the trial. The Court will accept and consider this post-trial filing as it relates to the issue of preemption. Preemption is an issue for the Court, not the jury. The post-trial filing removes an area of confusion identified by the Court in the summary judgment decision dated 12/23/03.

11. The 8/6/96 letter from defendant to the FDA contains minor revisions of an earlier label submitted in 1992. It confirms that in 1997, the FDA approved various label changes for Phenergan and rejected the language which defendant proposed in 1981 and 1988 concerning the preferred use of an intravenous infusion set for administering irritant drugs.

12. Plaintiff's expert witness Harold Green, M.D. testified that the warnings and instructions on the Phenergan label at the time of plaintiff's injury were inadequate to make the product safe because the defendant did not warn sufficiently of the risk of intravenous injection. Dr. Green testified that there was little medical justification for administration of Phenergan intravenously because of the availability of an intramuscular injection. If a physician chose intravenous administration of the drug, the use of a free-flowing IV bag would be safer than injection through a butterfly infusion set. Green Tr. 232-33.

13. Defendant's expert witness David Greenblatt, M.D. disagreed with Dr. Green. He testified that the clinician should remain free to decide whether to administer

Phenergan intravenously instead of by intramuscular injection. Greenblatt, Tr. 26-27. Dr. Greenblatt agreed with Dr. Green that it was safer to administer Phenergan through a free-flowing IV than by direct intravenous injection. Greenblatt, Tr. 49. Dr. Greenblatt testified that the butterfly infusion set could be considered to be a form of free-flowing IV administration. Greenblatt, Tr. 49.

Analysis

In any preemption case, the only issue is whether Congress intended to exercise the authority provided by the Supremacy Clause to serve as the exclusive source of law. U.S. Const. art. VI, cl. 2; see also M. Carrier, *Federal Preemption of Common Law Tort Awards by the Federal Food, Drug, and Cosmetic Act*, 51 Food & Drug L.J. 509, 510-11 (1996). In a system in which federal and state law frequently overlap and occupy the same ground, the Supreme Court has consistently required restraint from the lower courts in striking down state remedies. See, e.g., *Silkwood v. Kerr-McGee Corp.*, 464 U.S. 238, 249-57 (1984) (allowing state court imposed punitive damages against nuclear rod manufacturer despite extensive federal regulation over atomic energy). The issue is defined by and limited to the search for Congressional intent expressed in specific legislation. Preemption analysis does not depend upon whether a judge believes that federal regulation of conduct is preferable for reasons of consistency or greater technical expertise.

The starting point for any analysis is the basic assumption that Congress did not intend to displace state law in passing legislation. *Maryland v. Louisiana*, 451 U.S. 725, 746 (1981). "Thus, while state action is preempted if it specifically frustrates the objectives, narrowly and

concretely defined, that underlie federal enactments, no such conclusion follows where the most that can be said is that the direction in which state law pushes someone's actions is in general tension with broad or abstract goals that may be attributed to various federal laws or programs." L. Tribe, American Constitutional Law 1187 (3d ed. 2000). The Supreme Court has stated that there is a strong presumption that "the historic police powers of the States [are] not to be superseded by Federal Act unless that [is] the clear and manifest purpose of Congress." *Rice v. Santa Fe Elevator Corp.*, 331 U.S. 218 (1947); but cf. *Hines v. Davidowitz*, 312 U.S. 52 (1941) (finding federal supremacy in the field of foreign affairs preempted a Pennsylvania statute requiring foreign aliens to register). In areas of health and safety, the U.S. Supreme Court has long recognized the primary interest of the states in the protection of their citizens. *Florida Lime & Avocado Growers v. Paul*, 373 U.S. 132, 144 (1963).

Congress has enacted preemption legislation in other related fields such as medical devices, 21 U.S.C. § 360k, and cigarette labeling, 15 U.S.C. § 1334, but it has not passed any legislation creating an area of *express* preemption for pharmaceutical labeling. See *Hurley v. Lederle Labs.*, 863 F.2d 1173, 1176 (5th Cir. 1988) (collecting decisions finding no express preemption for pharmaceutical labeling). When Congress has not enacted an express preemption provision, the courts must consider whether its intent to preempt state law can be fairly *implied*. The traditional bases for *implied* preemption are: (1) a comprehensive regulatory scheme which occupies the field so completely as to leave no room for state action (field preemption); (2) state law which obstructs the purpose of federal legislation (obstruction conflict preemption); or (3) a direct conflict

between state and federal law (direct conflict preemption). *Hillsborough County, Fla. v. Automated Medical Laboratories*, 471 U.S. 707, 713 (1985). Under this standard, defendants argue that the breadth of FDA activity and the potential for interference with its regulatory decisions creates a basis for *implied* preemption. The breadth of activity is a basis for a claim of *field* preemption. The potential for interference is a basis for claims of *conflict* preemption. The Court will address each separately.

Field Preemption

Since 1906, the Food and Drug Administration—then functioning as the Bureau of Chemistry—has reviewed and approved pharmaceutical labels under Congressional authority. 1906 Food and Drugs Act, ch. 3915, 34 Stat. 768 (repealed by the Federal Food, Drug, and Cosmetic Act of 1938, codified at 21 U.S.C. §§ 301 *et seq.* (2000)). The regulation of labeling is mandatory. Even minor changes require FDA approval. At the same time that the FDA has regulated pharmaceutical labels, plaintiffs in every state have filed tort claims against drug manufacturers on common law causes of action—principally strict liability for failure-to-warn. See, e.g., *McCallister v. Purdue Pharma L.P.*, 164 F. Supp. 2d 783, 787 (S.D. W. Va. 2001).

FDA regulation and state law tort remedies have coexisted for decades—generally to the consternation of the manufacturers. Despite countless "failure-to-warn" cases, filed over several decades, defendants have not identified an authoritative line of cases in which FDA regulation of pharmaceutical labels has been held to preempt the state law remedy of strict liability.

The evidence in this case demonstrates that FDA regulation of labeling is mandatory and comprehensive. It

has long operated in conjunction with state law tort claims. Both the Restatement (Second) and Restatement (Third) of Torts: Product Liability permit manufacturers to offer evidence of compliance with FDA requirements as evidence of lack of defect. Restatement (Third) of Torts: Product Liability § 4 (1998); Restatement, Second, of Torts § 288c. (1965). Compliance with the FDA regulations alone has never been held to be a bar as a matter of law to state law claims that a manufacturer failed to provide an adequate warning. Compare *Caraker v. Sandoz Pharmaceuticals Corp.*, 172 F. Supp. 2d 1018, 1030-39 (S.D. Ill. 2001), with *McCallister*, 164 F. Supp. 2d at 792-93 (noting some preemption implications of the Controlled Substances Act).

The absence of an express preemption provision in the enabling legislation for FDA regulation is strong evidence that Congress has chosen not to preempt state law remedies in the area of pharmaceutical labeling. Cf. *Jones v. Rath Packing Co.*, 430 U.S. 519, 537 (1977) ("If Congress had intended to overrule this longstanding ... practice, founded on a legislative statement of necessity, we would expect it to have done so clearly."); but cf. *Hurley*, 863 F.2d at 1179 (suggesting that the pervasiveness of FDA label regulations would preempt state action involving the adequacy of vaccines warnings). The *express* preemption provisions for medical devices, 21 U.S.C. § 360k, cigarettes 15 U.S.C. § 1334, and pesticides 7 U.S.C. § 136v(b), (FIFRA), demonstrate that Congress knows how to enact preemptive legislation when necessary. See *Cipollone v. Liggett Group, Inc.*, 505 U.S. 504, 518-20 (1992) (interpreting express statutory preemption). These are obviously different than the implied preemption cases because Congress has spoken aloud and expressly on the issue.

The great majority of courts considering the issue have held that state law claims are not preempted by the dominant presence of the FDA in the field. See *Caraker*, 172 F.Supp. 2d at 1038-39; *Foyle v. Lederle Labs.*, 674 F.Supp 530, 533 (E.D.N.C. 1987); *Carlin v. Superior Court*, 920 P.2d 1347, 1352-53 (Cal. 1996); *Washington State Physicians Ins. Exch. & Assoc. v. Fisons Corp.*, 858 P.2d 1054, 1069 (Wash. 1993); *Feldman v. Lederle Labs*, 625 A.3d 1066, 1070 (N.J. 1993); *Plenger v. Alza Corp.*, 13 Cal.Rptr. 2d 811, 819 n.7 (1992); but see *Ehlis v. Shire Richwood, Inc.*, 233 F. Supp. 2d 1189, 1197-98 (D.N.D. 2002) (dicta suggesting preemption through the medical device amendment might apply). The sheer number of these decisions demonstrates that this is not a new issue on which Congress has not had an opportunity to act.

The requirement that pharmaceutical labels be approved by the FDA is insufficient to overcome the presumption against implied preemption. This Court finds no basis for denying plaintiff her remedies under state law on the basis of field preemption.

Conflict Preemption—Obstruction

Whether state law damage claims actually impede the FDA in the pursuit of its mission is hard to see from the limited context of a single personal injury trial. Successive political administrations have differed on this issue. In 1998, the FDA posted its final version of new rules governing the labeling of prescription drugs and clarified that the rules did not in any way preempt tort liability or a manufacturer's duty to warn. *Prescription Drug Product Labeling; Medication Guide Requirements*, 63 Fed. Reg. 66378, 66383-84 (Dec. 1,1998). More recently, the FDA has had occasion to take the opposite position. Brief of Amicus Curiae

United States, *Motus v. Pfizer, Inc.*, 358 F.3d 659 (9th Cir. 2004) (Nos. 02-55372, 02-55498) (urging the court to affirm summary judgment because FDA regulations preempted plaintiff's duty to warn claim).

The perception of the administrative agency that its work is obstructed is not the standard at issue. Cf. *INS v. Cardoza-Fonseca*, 480 U.S. 421 (1987); *Chevron U.S.A., Inc. v. Nat. Resources Def. Council*, 467 U.S. 837 (1984) (rejecting outright deference to an agency's statutory interpretation in favor of an analysis of congressional intent and traditional statutory construction). It is only the intention of Congress that matters. See *Jones*, 430 U.S. at 525. Many agencies may believe that they possess comprehensive expertise in their field and that any requirement of law arising from another source interferes with their work.

Some tension between the FDA and common law tort remedies is natural, inevitable, and probably healthy. The two sources of law function to meet very different concerns. The tort process does not propose to provide policy and rules applicable to the entire pharmaceutical industry. Instead, it is concerned with compensating individuals for wrongs and providing pressure to curb negligent behavior and the sale of defective products. The FDA regulatory process does not propose to provide compensation in individual cases. Instead, it seeks to provide rules concerning testing, developing and labeling of pharmaceutical drugs which apply to all companies.

The record in this case does not indicate that the work of the FDA has been obstructed by the potential exposure of the manufacturer to state law tort liability. The evidence in this case is that a concern about inadvertent intra-arterial injection surfaced by 1979 and was

the subject of a relatively mild warning proposed by the defendant in 1981 and again in 1988. The FDA rejected the proposed labeling change 9 years later in 1997 in a brief comment. There is no evidence in this record that either the FDA or the manufacturer gave more than passing attention to the issue of whether to use an IV infusion to administer the drug. The proposed labeling change did not address the use of a free-flowing IV bag. Viewing the matter in hindsight through the lens of a single catastrophic case, this Court heard little evidence that the FDA reviewed the issue of the intravenous administration of Phenergan with scientific rigor or any sense of urgency.

This record is very different from the type of intensive regulation described by the Justice Department in their brief submitted in a May 2004 medical device case (*Horn v. Thoratec*). Ex. A to Wyeth's Memo dated 4/16/04. In that brief, the government described a comprehensive pre-market approval process for medical devices requiring an average of 1,200 hours of review time by the agency, thousands of pages of documentation, and substantial give-and-take between the agency and the manufacturer. Brief at p. 8, 21. According to the Justice Department, revision of an existing PMA follows an equally stringent and rigorous process. That is a very different process from the leisurely course of review for the Phenergan label changes conducted over some sixteen years. The regulatory process in this case was marked by long periods of dormancy and a conclusory decision in 1997 to require no change to the existing label. The recommendation of administration through a free-flowing IV bag never appears in the regulatory record. In short, a tort case is unlikely to obstruct the regulatory process when the record shows

that the FDA has paid very little attention to the issues raised by the parties at trial.

The principal basis for obstruction advanced by proponents of implied preemption in the pharmaceutical field is concern that excessive or unwarranted warnings will reduce the use of a safe and valuable medication. See Justice Department Brief in *Horn v. Thoratec* at 25-26; R. Pear, *In a Shift, Bush Moves to Block Medical Suits*, N.Y. Times, July 25, 2004, available at http://www.nytimes.com/2004/07/25/politics/25DRUG.html. The problem of "defensive warning" is not strong in this case. Any warning or instruction about the greater safety of a free-flowing IV bag relates only to the method of administration, not to the decision to use Phenergan. This case is different from cases involving proposed warnings of remote side effects which might dissuade physicians from using the drug to the detriment of the patient population.

There is no basis in this case to conclude that the work of the FDA was obstructed in any way by the indirect pressure of state law tort liability.

Conflict Preemption—Direct Conflict

The FDA regulations and a state law failure-to-warn case do not conflict directly. Compliance with the FDA labeling regulations is not a complete defense, but the manufacturer is entitled to raise it as a defense as defendant has done in this case. Restatement (Third) of Torts: Product Liability § 4. The record in this case is mixed concerning the ability of the defendant to provide a sharper warning about the risks of intravenous injection. While the defendant insisted that severe sanctions, including criminal prosecution, would follow any change to the label as approved by the FDA in 1981 and 1997, the FDA regulations permit strengthened

warnings without approval on an interim basis. 21 C.F.R. 314.70; see also *Kurer v. Parke, Davis & Co.*, 679 N.W. 2d 867, 872-74 (Wis. App. 2004).

More fundamentally, compliance with federal regulation does not provide a complete defense against tort liability. In a three-member partially dissenting opinion in *Cipollone v. Liggett Group*, 505 U.S. 504 (1992), Justice Blackmun wrote:

> The effect of tort law on a manufacturer's behavior is necessarily indirect. Although an award of damages by its very nature attaches additional consequences to the manufacturer's continued unlawful conduct, no particular course of action (*e.g.*, the adoption of a new warning label) is required. A manufacturer found liable on, for example, a failure-to-warn claim may respond in a number of ways. It may decide to accept damages awards as a cost of doing business and not alter its behavior in any way. Or, by contrast, it may choose to avoid future awards by dispensing warnings through a variety of alternative mechanisms, such as package inserts, public service advertisements, or general educational programs. The level of choice that a defendant retains in shaping its own behavior distinguishes the indirect regulatory effect of the common law from positive enactments such as statutes and administrative regulations. Moreover, tort law has an entirely separate function—compensating victims—that sets it apart from direct forms of regulation.

Id., 505 U.S. 536-37 (citations omitted). There is no direct conflict between the FDA regulatory process and

the common law remedy. The record in this case was that there have been at least 20 reports of amputations similar to plaintiff's injury since the 1960s. Green, Tr. 216. The defendant has remained in compliance with the FDA regulations by retaining the same warning about the risks of intra-arterial injection for several decades. This warning may be insufficient—certainly this jury found it to be so—and the result is that on some occasions the defendant may pay compensation. This tension does not amount to a direct conflict with the FDA labeling requirements. "The reason why many courts find no preemption is that the FDA's drug labeling decisions impose only 'minimum' standards that are open to supplementation by state law through a jury's verdict enforcing a manufacturer's common law duty to warn." *Caraker*, 172 F. Supp. 2d at 1033. The record in this case of a slow and imperfect regulatory process illustrates why courts have consistently held that FDA regulation provides a minimum standard of safety.

This Court finds no basis for federal preemption on grounds of direct conflict.

II. Causation

Defendant seeks to attribute sole causation as a matter of law to the actions of Jessica Fisch, P.A. who continued to inject the Phenergan despite a statement from the plaintiff that the injection hurt. This argument raises factual issues which were argued to the jury and resolved in plaintiff's favor at trial.

First, there is a factual dispute about whether it was too late for Ms. Fisch to stop the injection if the burning sensation experienced by the plaintiff was the Phenergan entering an artery. Second, the defendant requested and received a detailed instruction on effi-

cient intervening cause, which addressed the same issues raised in this motion. Third, and most importantly, warnings are almost never the *sole* cause of an injury. Injury occurs only after the warning combines with human conduct to produce at least two concurrent causes of the event. *Gilman v. Towmotor Corp.*, 160 Vt. 116, 119-20 (1992); see also Restatement (Third) of Torts: Product Liability § 2 cmt. m (foreseeability); *id.* at § 16 (increased harm due to product defect). The warning is read—or not—by some human actor who follows it—or not. If subsequent human action were enough to break the chain of causation, there would be no cause of action for failure-to-warn. Restatement (Third) of Torts: Product Liability § 17.

The plaintiff's claim is not that Ms. Fisch was without blame or fault. Rather, as this Court understands it from trial, the claim is that if Ms. Fisch and her supervising physician had been told of the risk of limb death and amputation, she would have administered Phenegan by a safer method than the butterfly infusion set. In rejecting the defense of efficient intervening cause, the jury decided that any conduct by Ms. Fisch did not break the chain of causation. There is sufficient evidence from Ms. Fisch, Dr. Matthews, and Dr. Green to support the jury's conclusion. This evidence is principally the testimony from Dr. Matthews that he would never have permitted administration of Phenergan through direct injection at his clinic if he had known of the risks to the patient and the testimony from Dr. Green that use of a free-flowing IV bag or intramuscular injection are safer methods of administering the drug.

Plaintiff argued at trial that a safer method of administration would have greatly reduced the risk of injury from inadvertent arterial injection. The defendant ar-

gued that injection through the butterfly-infusion set remains an appropriate method of administration. The jury rejected this defense and accepted the plaintiff's version of the facts. The Court will not overturn the verdict on a factual issue when there is evidence to support the jury's conclusion.

III. Damages

Defendant seeks a new trial for damages on the grounds that the Court did not grant a present value instruction for general damages (non-economic damages), which resulted in an oversized general damages award ($5,000,000). No challenge is raised to the award of special damages (medical and rehabilitative expenses and lost income) in the amount of $ 2.4 million.

A. Present Value Instruction

In this case, the Court rejected defendant's request for an instruction that any award of future general damages should be reduced to present value. There were several reasons for this.

First, the defendant put on no proof or argument concerning how to reduce future pain and suffering to present value. Nor, of course, did plaintiff. Future *economic* damages were always reduced to present value by plaintiff's economist and were essentially conceded without challenge by defendant. See, e.g., *Girroir v. Carpenter*, 136 Vt. 290, 292 (1978); *Wolfe v. Mendel*, 84 N.W.2d 109, 111, 115 (Neb. 1957) ("Where an instruction does not prohibit or negative the computation of damages upon the basis of their present worth, it will not be assumed that the jury did not understand that it was to estimate the present value of future earnings lost."). The defense never proposed a method by which the jury could discount for prevailing interest rates

while accounting for the effects of expected inflation. Even the 12 % discount rate proposed in the post-trial briefs was not suggested.

The briefing on this motion illustrates the practical difficulties of instructing the jury in a meaningful fashion that they should reduce the award of future pain and suffering to present value. The lawyers have presented wildly different proposals and methodologies. The defendant proposes a simple discount rate based on 12 % or 2 %. It offered no economic opinion at trial.

On the evidentiary record alone, including closing arguments, there was an inadequate basis for a present value instruction on future pain and suffering.

Second, the majority view—starting with the Restatement (Second) of Torts § 913A cmt. a—is that the calculation of future general damages is too subjective to be subjected to economic analysis by a lay jury. *Flanigan v. Burlington N., Inc.*, 632 F.2d 880, 886 (8th Cir.1980); *O'Byrne v. St. Louis Southwestern Ry. Co.*, 632 F.2d 1285, 1286 (5th Cir.1980); *Taylor v. Denver & Rio Grande W. R.R.*, 438 F.2d 351, 353 (10th Cir.1971) ("[T]he courts [have] held that the better reasoned authority supports the rule that future pain and suffering should not be reduced to current worth."); *United States v. Harue Hayashi*, 282 F.2d 599, 605-06 (9th Cir.1960); *Texas & Pacific Railway Co. v. Buckles*, 232 F.2d 257, 264 (5th Cir. 1956); *Chicago & N.W. Ry. Co. v. Candler*, 283 F. 881, 885 (8th Cir. 1922) ("The arbitrariness and artificiality of such a method is so apparent that to require a jury to apply it would, we think, be an absurdity."); *Purdy v. Belcher Refining Co.*, 781 F.Supp. 1559, 1563 (S.D.Ala.1992); *Hanson v. Reiss Steamship Company*, 184 F.Supp. 545, 552-53 (D.Del.1960) (holding that allowances for future pain

and suffering are not subject to reduction to present worth); *Sleeman v. Chesapeake & O. Ry. Co.*, 305 F.Supp. 33, 36 n.1 (W.D.Mich. Sep 09, 1969) vacated, 424 F.2d 547 (6th Cir. 1970); *Schirra v. Delaware, L. & W.R. Co.*, 103 F.Supp. 812, 824 (M.D.Pa.1952); *Beaulieu v. Elliott*, 434 P.2d 665, 671-72, 676 (Alaska 1967); *Braddock v. Seaboard Air Line R.R.*, 80 So.2d 662, 666-68 (Fla.1955); *Delva v. Value Rent-A-Car*, 693 So.2d 574, 578 (Fla.App. 1997); *Bagley v. Akins*, 138 S.E.2d 430, 431 (Ga.App. 1964); *Brant v. Bockholt*, 532 N.W.2d 801, 803-04 (Iowa 1995) (collecting cases); *Louisville & N.R. Co. v. Gayle*, 263 S.W. 763 (Ky. 1924); *Busch v. Busch Const., Inc.*, 262 N.W.2d 377, 397 (Minn. 1977); *Barlage v. The Place, Inc.*, 277 N.W.2d 193, 195 (Minn.Sup.Ct. 1979); *Dickerson v. St. Louis S.W. Ry.*, 697 S.W.2d 210, 212 (Mo.App.1985); *Ball v. Burlington N. R.R.*, 672 S.W.2d 358, 361 (Mo.App.1984); *Porter v. Funkhouser*, 382 P.2d 216, 218-19 (Nev. 1963); *Friedman v. C & S Car Serv.*, 527 A.2d 871, 873-75 (N.J. 1987); *Bready v. Tipton*, 407 P.2d 194, 206 (Okla. 1965); *Yost v. West Penn. Ry Co.*, 9 A.2d 368, 369-70 (Pa. 1939); *Missouri Pac. R.R. v. Handley*, 341 S.W.2d 203, 205 (Tex.Civ.App. 1960); *Borzea v. Anselmi*, 258 P.2d 796, 804 (Wyo. 1952); 22 Am. Jur. 2d *Damages* § 999 ("[T]he generally accepted rule is that the award [for pain and suffering] is not to be thus reduced [to present worth]."); see also *Oliveri v. Delta S.S. Lines, Inc.*, 849 F.2d 742, 750-52 (2d Cir. 1988) (noting that the majority of state jurisdictions do not reduce future pain and suffering awards and criticizing the rule requiring reduction to present value); *Hogan v. Santa Fe Trail Transportation Co.*, 85 P.2d 28, 34-38 (Kan. 1938) (Wedell, J., dissenting) (collecting early cases); *McKenna v. State*, 492 N.Y.S.2d 805, 807 (1985).

Third, it would involve the Court and the jury in something of a charade to pretend that without expert guidance, the jurors are capable of running accurate present value calculations on general damage awards proposed during deliberations. Judges and lawyers are universally incapable of performing the discount calculations with or without a calculator and the tables of historic interest rates and inflationary factors. It is invariably the topic of expert testimony by an economist, and then only on the elements of special damage such as lost income and future medical bills. As Professor Dobbs succinctly states the issue:

> The Rule requiring reduction to present value must be qualified in several ways. In the first place, viewed realistically, the plaintiff is often not required to put on proof or explanation how reduction is to take place, and if the jury only gets an instruction to make the reduction without any further explanation, the rule probably does not mean very much. Beyond this, there is the agreed limit to the rule that only pecuniary losses are reduced. Thus awards for future pain and suffering, or for the future loss of companionship or guidance, are made without reduction. Presumably this is because it would be futile and even misleading to compute mathematically a reduction on an award that could have no mathematical basis in the first place.

D. Dobbs, *Handbook on the Law of Remedies* § 8.7, at 574 (1st ed. 1973).

For this reason, the Vermont Supreme Court has limited *pre-judgment* interest to special damages. *Gilman*, 160 Vt. at 121; see also *Bull v. Pinkham Eng'g*

Assoc., 170 Vt. 450, 463-64 (2000); *Ulm v. FordMotor Co.*, 170 Vt. 281, 292-94 (2000); *Remes v. Nordic Group, Inc.*, 169 Vt. 37, 40-41 (1999); *Estate of Fleming v. Nicholson*, 168 Vt. 495, 501-03 (1998); *Winey v. William E. Dailey, Inc.*, 161 Vt. 129, 141 (1993); *Turcotte v. Estate of LaRose*, 153 Vt. 196, 198-200 (1989). It would be uneven at best to eliminate pre-judgment interest on general damages while requiring a reduction for future awards. Cf. Restatement (Second) of Torts § 913A cmt. a (linking present worth valuations with § 912 and its prohibition on prejudgment interest for pain and suffering). The reasoning that it is

The Court will not grant a new trial on the basis of the jury charge on general damages.

B. Reasonableness of the general damage award

Defendant cites several Vermont verdicts ranging from $1 million to $3 million recorded between 1977 and 1999. Defendant argues that at $5 million for general damages, this verdict is too high. Defendant does not take issue with the award of $2.4 for special damages and did not challenge the proof on that issue at trial.

This Court will not remit or set aside the damages verdict because the damage award is reasonably supported by the proof at trial. *Dean v. Arena*, 141 Vt. 647, 650 (1981). Several factors support a high award for pain and suffering.

First, this was an extraordinary case. The defendant describes it as tragic, and the Court saw it the same way at trial. The proof of plaintiff's joy and commitment to music prior to the loss of her arm was very compelling. The immediate effects of the injury were horrific. The changes in plaintiff's life as a result of her injury are wide and deep. This was as bad an injury

case as any court is likely to see. What made the case unusual was the way that the injury cut so directly into the life of a musician. The evidence of plaintiff's suffering and the loss of her ability to play the guitar at a professional level was powerful and undisputed.

Second, the jury verdicts presented by defendant place this verdict at one end of a range of results in serious cases in Vermont. So far as it is possible to tell, this jury verdict is the largest to date in a personal injury case. The verdicts are necessarily incomplete because they do not include settlements. This information is available only at third-hand, but it is generally known within the Vermont legal community; over the course of the last 10 years, a few severe injury cases have settled for amounts in excess of the verdicts listed by defendant. In October 2002, the Lamoille Superior Court entered judgment in a case involving quadriplegia for $48,000,000 following a bench trial. *Perron v. Vt. Utility Serv. Inc.*, No. 154-8-01LeCv (Cashman, J., Oct. 2002). On April 8, 2004, the Addison Superior Court entered judgment for $2,345,764 after a damages hearing in a default case concerning a severe foot injury. *Hadvab v. Manning*, No. 121-6-03 Ancv, 8 Vt.TrialCt.Rep. 274 (Toor, J.). This Court does not rely on these results in any direct evidentiary fashion because the underlying facts are not available for comparison, but they do provide some indication that a $7.4 million dollar verdict is not an isolated event within our legal culture.

The standard for review of a damages award is whether the award is "entirely excessive" or "shocks the conscience." *Turgeon v. Schneider*, 150 Vt. 268, 274 (1988); *Newhall v. Central Vermont Hospital*, 133 Vt. 572,576-77 (1975). This was a bad damages case. The defendant chose not to challenge the damages at trial. The verdict

falls within a range of results seen in recent years in our state. This Court finds that the verdict is reasonably supported by the evidence and is not excessive for purposes of Rule 50 or Rule 59(a).

CONCLUSION

Defendant's motion for judgment under Rule 50 or, in the alternative, for a new trial on damages is DENIED.

Dated: 7-30-04

/s/_____
Superior Court Judge

STATE OF VERMONT

WASHINGTON COUNTY, S.S.

LEVINE)

-v-)

WYETH)

TAPED HEARING

-before-

THE VERMONT SUPREME COURT

Taken on October 5, 2005

Supreme Court Building

Montpelier, Vermont.

* * *

[7] [MR. REIN] supremacy clause of the constitution. This issue is raised below in several times and it was adjudicated as a matter of law, and it's properly before this Court for de novo review as a matter of law.

I want to emphasize to the Court that issue as presented here is very narrow and very particularized. It's what is called a conflict preemption issue, a collision between state and federal requirements on the specific labeling of Phenergan. It's focused on Phenergan in the facts of this case. Wyeth is not contending for a field preemption, for the ouster of Vermont law, tort law,

not at issue here. Wyeth is not contending that the mere compliance with the federal—

FEMALE JUSTICE: You have briefed those issues, so I want to make sure I understand, you are no longer contending field preemption?

MR. [REIN]: We did brief them below but not in this Court. This is conflict preemption, not field preemption. We have said that the background of intense federal regulations lends weight to the conflict preemption. We are not arguing for conflict preemption nor are we arguing that the mere compliance with the federal labeling requirements in and of itself creates a conflict preemption, contending on the specific duties at issue here.

[8] Um, and so the question the Court must focus on is where is the conflict? What are we talking about? And let's put it as simply as possible. Vermont law as formed and applied at the trial Imposed on Wyeth a labeling duty, a duty to label in a particular way which in our view and in our brief would have shown would have forced Wyeth to commit a prohibited act under federal law. And even if you assume that it wasn't a prohibited act, would have required Wyeth to take an action which would have frustrated the objects and purposes of FDA regulation.

* * *

[10] says that [Geier] is overruled or that [Cipollone] is overruled and [Cipollone] is the smoking case where the Supreme Court first said: "A duty imposed by state law, albeit through the tort system, is a duty which has to be judged in conflict preemption. And Bates really turned on statutory preemption because there is statutory language in Bates which was put at

issue, very similar to the medical device amendment, so it's a slightly different case. And so—

MALE JUSTICE: If I can interrupt. So what procedure or course would your client have had with regard to FDA upon a denial, as you've characterized it, of the CBE, the change in the notice, to get out of the box, so to speak, administratively?

MR. [REIN]: I think that really gets to the heart of the matter. You have to ask where our client was. What we were being told in the plaintiff's brief was that Wyeth was negligent, and I'm quoting from page 11, "because the label failed to instruct that any IV administration be through a free-flowing IV system or not at all." So that was the duty that was imposed by Vermont law at the plaintiff's request.

From a federal point of view, Wyeth submitted a supplemental application to the FDA which was ruled on by the FDA in 1997, and when the FDA ruled on it, they said,

* * *

[17] [MR. RUBIN] role to play in protecting its citizens in health and safety. There is a presumption against preemption, and a particular presumption against it in cases like this.

So what do they have to prove? They have to prove by clear evidence that a conflict is irreconcilable and it is impossible for Wyeth to both comply with the label and comply with Vermont common law that safe drugs be given to patients in Vermont.

FEMALE JUSTICE: But what about the argument that what is different in this case is that they asked to change the label and the FDA issues this language that says retain verbiage on the current label or

retain current verbiage or something like that. Does that make a difference from all those other cases?

MR. [RUBIN]: No, it doesn't, because what our case was essentially is quite simple. This drug is safe if it's injected intramuscularly. Four witnesses testified, Do not inject Phenergan IV push. Do not push it directly into a vein. That was the instruction that we wanted and that was the instruction that the jury found was necessary. So let's look at what in fact the FDA rejected. The first instruction says when administrating any irritant drug intravenously, it's usually preferable to inject (unclear) et cetera, et cetera. There is nothing in this language which precludes IV push. This

* * *

[21] method of administration of drugs or just to the—

MR. [RUBIN]: No. I think it's misrepresenting that the drug—

FEMALE JUSTICE: —elements of the drug itself, or the usefulness or the drug itself. Is there any distinction to be made there?

MR. [RUBIN]: Yeah. I think misbranding is that drug will do something that it can't do or be used for something that it shouldn't be used for. But if they want a conflict preemption here, they need a document, and you look at this document here, it's from the FDA and they say we considered the IV push method of injection. We think that you must include the option of IV push in your label because we believe that the patients who get your drugs should have that option. That is what they need, something like that. That would be clear evidence of a conflict.

As both trial judges said in this case, there is nothing in the record. What they have is a letter that says use the current verbiage. That is the record.

MALE JUSTICE: What about the argument, it's not just enhancing the safety warning, but in effect it's removing from professional availability a procedure, however risky, which had been recognized as available? You know.

LETTER FROM FDA TO WYETH DATED AUGUST 26, 1955 (DEFENDANT'S SUMMARY JUDGMENT EXHIBIT B)

DEPARTMENT OF
HEALTH, EDUCATION, AND WELFARE
FOOD AND DRUG ADMINISTRATION
WASHINGTON 25, D. C.

Stamp: AUG 26 1955

NDA 8857

Wyeth Laboratories, Inc.
Attention: Dr. Ashkenaz
1401 Walnut Street
Philadelphia, Pa.

Gentlemen:

This will acknowledge your communications of July 5, 1955, July 8, 1955 and July 29, 1955, submitting additional material pertinent to your new drug application 8857 for your product "Injection Phenergan Hydrochloride".

It is understood as discussed with your representative Dr. Ashkenaz in person on June 21, 1955 and by telephone on August 22, 1955 that translations of the various French articles will be submitted to complete the requirements under section 505(b)(1) of the Federal Food, Drug and Cosmetic Act.

It is understood as discussed with Dr. Ashkenaz by telephone on July 5, 1955 that the second sentence of the first paragraph under "Indications" in the revised brochure will be changed to read as follows: "Injection

Phenergan Hydrochloride' has also proven useful as a sedative particularly when used as preanesthetic medication". This involves deletion of the references to "prevention of post-operative nausea and vomiting" and to "use with meperidine and chlorpromazine in hibernation anesthesia".

We are taking action on this application with the understanding that these things will be done.

We have completed our study of this application and in accordance with the provisions of the regulation under section 505(c) of the Act it has become effective.

Please submit five copies of the final printed label and labeling and three finished market packages of the drug when available.

Sincerely your,

/s/

Barbara Moulton, M.D.
Medical Officer
New Drug Branch
Division of Medicine

INTERNAL WYETH MEMORANDUM DATED FEBRUARY 17, 1967 (PLAINTIFF'S SUMMARY JUDGMENT EXHIBIT 15)

INTERNAL CORRESPONDENCE

[logo]

to William E. Langeland, Ph.D.	from Walter H. Comer, M. D.
company W L D located Radnor	company W L D located Radnor
subject Phenergan® Adverse Reaction	date February 17, 1967

Lt. Colonel Harry Cerha
Headquarters, AFMSTC
Washington, D.C. 20333

Dear Bill:

Lt. Colonel Harry Cerha informed us of an adverse reaction occurring in a woman during labor involving three drugs given intravenously in a single injection. These drugs are Demerol®, Leritine® and Phenergan. A severe arteriospasm resulted during the injection, acceptable treatment, the spasm continued, resulting in gangrene of the arm and subsequent amputation.

The information from Colonel Cerha was given in a phone conversation February 15, 1967, and is not complete. The incident occurred some time in 1965. This information is being presented to the Food and Drug Administration because it is the first such incident reported to us involving Phenergan.

Phenergan was given (50 mg.) IV in a dose not recommended in the approved Phenergan direction circu-

lar. The direction circular also gives warning against perivascular extravasation and also includes a warning against intra-arterial injection.

Information reached us because of an allegation on the part of the patient against the Air Force.

Sincerely,

/s/

Walter H. Comer, M. D.

WHC:jda

Enclosure—Drug Reaction Report

cc: Mr. Smythe
Mr. Deuble
Dr. Shaw
Medical Routing
File

[illegible stamp]

[logo]

LETTER FROM FDA TO WYETH DATED AUGUST 5, 1974 (DEFENDANT'S TRIAL EXHIBIT P)

[logo]

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
ROCKVILLE, MARYLAND 20852

NDA 8-857/S-003

Stamp: AUG 5 1974

Stamp: RECEIVED
AUG 8 1974
[illegible]

Wyeth Laboratories, Incorporated
Attention: W. E. Langeland, Ph.D.
P.O. Box 8299
Philadelphia, Pennsylvania 19101

Gentlemen:

We acknowledge the receipt on March 26, 1974, of your communication dated March 19, 1974, regarding your supplemental new drug application of December 18, 1973, submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for Phenergan (promethazine hydrochloride) Injection.

The supplemental application provides for revised labeling.

We have completed the review of this submission and conclude that convulsions can occur with therapeutic doses of phenothiazines so it would be misleading to list this reaction only under the overdosage section in association with suicide attempts. We also recommend the following changes in the "Revised July 26, 1973" package insert:

Under the heading Actions; delete the words "that has" and insert "with the", and add the phrase "characteristics of this class of drugs." Also, delete the phrases "which is of marked potency and prolonged duration" and "so that it is useful in a variety of clinical situations."

Under the heading Warnings, change the first sentence in the third paragraph to: "The intravenous use of promethazine is not without hazard." In addition, add the sentence/paragraph: "The safety of Phenergan in women who are or may become pregnant has not been established; hence it should be given only when the potential benefits have been weighed against the possible hazards to mother and child."

Under the heading Adverse Reactions, change the first sentence in the second paragraph to: "Cases have been reported where patients receiving promethazine have developed leukopenia, and agranulcytosis". The next sentence should read: "In nearly every instance reported other toxic agents have been associated with the administration of promethazine. The third paragraph first sentence should be revised to: "Cardiovascular side-effects from promethazine have occurred. The phrase "although extremely rare" should be deleted from

the first sentence of the fourth paragraph. The word "rarely should be deleted from the first sentence of the fifth paragraph and the phrase "and convulsions", should be added to the end of the sixth or last paragraph.

Please let us know promptly your proposal in regard to the above recommendations.

Sincerely yours,

/s/

Barrett Scoville, M.D.
Director
Division of Neuropharmacological
Drug Products
Office of Scientific Evaluation
Bureau of Drugs

LETTER FROM WYETH TO FDA DATED DECEMBER 23, 1974 (DEFENDANT'S TRIAL EXHIBIT Q)

WYETH LABORATORIES INC. [logo] *Box 8299 , Philadelphia, Pennsylvania, 19101*

December 23, 1974

NDA 8-857/S-003

Barrett Scoville, M.D., Acting Director
Division of Neuropharmacological Drug Products
Office of Scientific Evaluation
Bureau of Drugs
Department of Health, Education and Welfare
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Dear Dr. Scoville:

Reference is made to our approved new drug application (NDA 8-857) for "Phenergan®, promethazine hydrochloride, Injection" and to your letter of August 5, 1974 regarding the package insert for this product.

We are pleased to provide herewith draft copy of this package insert for this product revised in accordance with the recommendations contained in your above referenced letter of August 5, 1974.

We trust that you will find these revisions satisfactory and will so inform us at your earliest convenience.

Sincerely,

WYETH LABORATORIES INC.

William E. Langeland, Ph. D.
Director, Project Coordination
Division

PVU:[illegible]
Encs.

cc: Dr. Bogash
Dr. Comer
Dr. Force
Dr. Gold
Dr. Lewis
Mr. McCarthy
Dr. Shaw
Mr. Smythe
Mr. Swenson
Mr. Welker

BEST AVAILABLE COPY

A.H.F.S. Category 4:00, 28:24, 68:20

Wyeth
Phenergan®
(promethazine hcl)
Injection

Description
Each cc. of injection contains either 25 mg. or 50 mg. promethazine hydrochloride with 0.1 mg. disodium edetate, 0.04 mg. calcium chloride and not more than 0.25 mg. sodium metabisulfite and 5 mg. phenol with sodium acetate buffer.

ACTIONS

Phenergan is a phenothiazine derivative with the characteristics of this class of drugs. In addition to its antihistaminic action it also provides antiemetic as well as sedative actions.

Indications
The injectable form of promethazine hydrochloride is indicated for the following conditions when use of the oral form is impractical:
Amelioration and prevention of allergic reactions to blood or plasma in patients with a known history of such reactions.
In anaphylaxis as an adjunct to epinephrine and other standard measures after the acute symptoms have been controlled.
For other uncomplicated allergic conditions of the immediate type when oral therapy is impossible or contraindicated.
Active treatment of motion sickness.
Preoperative, postoperative and obstetric (during labor) sedation.
Prevention and control of nausea and vomiting associated with certain types of anesthesia and surgery.
As an adjunct to analgesics for the control of postoperative pain.
For sedation and relief of apprehension and to produce light sleep from which the patient can be easily aroused.
Intravenously in special surgical situations, such as repeated bronchoscopy, ophthalmic surgery, and poor risk patients, with reduced amounts of meperidine as an adjunct to anesthesia and analgesia.

Contraindications
Phenergan is contraindicated in individuals with a known hypersensitivity to the drug.
Under no circumstances should promethazine hydrochloride be given by intra-arterial injection due to the likelihood of severe arteriospasm and the possibility of resultant gangrene.

Warnings
The sedative action of promethazine hydrochloride is additive to the sedative effects of central nervous system depressants; therefore, agents such as alcohol, barbiturates and narcotic analgesics should either be eliminated or given in reduced dosage in the presence of promethazine hydrochloride. When given concomitantly with promethazine hydrochloride the dose of barbiturates should be reduced by at least one-half and the dose of analgesic depressants, such as meperidine or morphine, should be reduced by one-quarter to one-half.

The preferred parenteral route of administration is by intramuscular injection. Subcutaneous injection is not recommended; evidence of chemical irritation has been noted and necrotic lesions have resulted on rare occasions following subcutaneous injection.

The intravenous use of promethazine is not without hazard.

Due to the close proximity of arteries and veins in the area most commonly used for intravenous injection, extreme care should be exercised to avoid perivascular extravasation or inadvertent intra-arterial injection. In such cases chemical irritation may be severe and spasm of digital vessels with resulting gangrene requiring amputation is a possibility.

When used intravenously, promethazine hydrochloride should be given in a concentration no greater than 25 mg per cc. and at a rate not to exceed 25 mg. per minute.

The safety of Phenergan in women who are or may become pregnant has not been established; hence it should be given only when the potential benefits have been weighed against possible hazards to mother and child.

Precautions

Ambulatory patients should be cautioned against driving automobiles or operating dangerous machinery until it is known that they do not become drowsy or dizzy from promethazine hydrochloride therapy.

Antiemetics may mask the symptoms of an unrecognized disease and thereby interfere with diagnosis.

Patients in pain who have received inadequate or no analgesia have been noted to develop "athetoid-like" movements of the upper extremities following the parenteral administration of promethazine. These symptoms usually disappear upon adequate control of the pain.

Adverse Reactions

Patients may occasionally complain of autonomic reactions such as dryness of the mouth, blurring of vision and, rarely, dizziness.

Cases have been reported where patients receiving promethazine have developed leukopenia and agranulocytosis. In nearly every instance reported other toxic agents have been associated with the administration of promethazine.

Cardiovascular side-effects from promethazine have occurred.

Minor increases in blood pressure and occasional mild hypotension have been reported.

Photosensitivity has been reported.

Occurrence of photosensitivity may be a contraindication to further treatment with promethazine or related drugs.

Attempted suicides with promethazine have resulted in deep sedation, coma, rarely convulsions and cardiorespiratory symptoms corresponding with the depth of sedation present. A paradoxical reaction has been reported in children receiving a single dose of 25 mg. to 50 mg., characterized by hyperexcitability and abnormal movements. Nightmares and respiratory depression have also been reported.

As with other phenothiazine drugs the following adverse reactions have been reported: extrapyramidal reactions (opisthotonos, oculogyric crisis, hyperreflexia, dystonia, parkinsonism) and convulsions.

Dosage and Administration

The preferred parenteral route of administration is by intramuscular injection. The proper intravenous administration of promethazine hydrochloride is well tolerated, but use of this route is not without some hazard; subcutaneous injection is not recommended (see Warnings).

ALLERGY: When the oral route is not feasible Phenergan® given intramuscularly or intravenously may be used. The average dose is 25 mg. The dose may be repeated within two hours if necessary, but oral therapy should be resumed if indicated and existing circumstances permit.

For children, single 25 mg. doses at bedtime or 6.25 to 12.5 mg. doses three times daily will usually suffice. After initiation of treatment in children or adults, dosage should be adjusted to the smallest amount adequate to relieve symptoms.

The administration of promethazine hydrochloride in 25 mg. doses prior to or during blood transfusion will prevent or control minor transfusion reactions of an allergic nature.

MOTION SICKNESS: The average adult dose for the active treatment of motion sickness is 25 mg. When oral medication cannot be tolerated, the dose should be given intravenously or intramuscularly. 12.5 to 25 mg. doses may be repeated as necessary at four to six hour intervals.

NAUSEA AND VOMITING: The average effective dose of Phenergan for the active therapy of nausea and vomiting associated with certain types of anesthesia and surgery is 25 mg. When oral medication cannot be tolerated, the dose should be given intravenously or intramuscularly. 12.5 to 25 mg. doses may be repeated as necessary at four to six hour intervals.

For prophylaxis of nausea and vomiting, as during surgery and the postoperative period, the average dose is 25 mg. repeated at four to six hour intervals as necessary.

For nausea and vomiting in children the dose should be adjusted to the age and weight of the patient and the severity of the condition being treated.

SEDATION: This product relieves apprehension and induces a quiet sleep from which the patient can be easily aroused. Administration of 12.5 to 25 mg. Phenergan at bedtime will promote sedation in children. Adults usually require 25 to 50 mg. for nighttime, preoperative or obstetrical sedation.

PRE AND POST OPERATIVE USE: Phenergan in 12.5 to 25 mg. doses for children and 50 mg. doses for adults the night before surgery relieves apprehension and produces a quiet sleep.

For preoperative premedication, children require doses of 0.5 mg. per pound of body weight in combination with an equal dose of meperidine and the appropriate dose of an atropine-like drug. Usual adult dosage is 50 mg. Phenergan with an equal amount of meperidine and the required amount of a belladonna alkaloid

For postoperative sedation and adjunctive use with analgesics, the dose is 12.5 to 25 mg. in children and 25 to 50 mg. in adults.

OBSTETRICS. Phenergan in doses of 50 mg. will provide sedation and relieve apprehension in the early stages of labor. When labor is definitely established, administer 25 to 75 mg. (average dose 50 mg.) promethazine hydrochloride intramuscularly or intravenously with 25 to 75 mg. meperidine (average dose 50 mg.). Amnesic agents may be administered as necessary. If the average doses of Phenergan and meperidine are used, it is seldom necessary to repeat the medication during a normal labor. If necessary, 25 to 50 mg. doses, with or without a reduced dose of analgesic, may be repeated once or twice, at three to four hour intervals.

How Supplied

Phenergan® (promethazine hydrochloride) Injection, 25 and 50 mg., is available in Ampuls of 1 cc.

Wyeth Laboratories Inc., Philadelphia, Pa. 19101
Printed U.S.A.

December 20, 1974

LETTER FROM FDA TO WYETH DATED MAY 4, 1976 (DEFENDANT'S TRIAL EXHIBIT R)

[illegible handwriting]

pc: Dr. Bogash
Dr. Gold
Dr. Langelan
Mr. Ross
Dr. Shaw
Mr. Smythe
Mr. Swenson

[logo]

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
ROCKVILLE, MARYLAND 20852

NDA 8-857/S-005

Stamp: MAY 04 1976

Stamp: RECEIVED
May 7 1976
[illegible]

Stamp: RECEIVED
May 10 1976
[illegible]]

Wyeth Laboratories
Attention: Earl T. Lewis, M.D.
P. O. Box 8299
Philadelphia, Pennsylvania 19101

Gentlemen:

Reference is made to your supplemental new drug application of November 14, 1975 submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for PHENERGAN(R) (promethazine hydrochloride) Injection.

The supplemental application provides for a revised package insert as discussed in our conference of August 25, 1975 and in our letter of August 29, 1975.

We have completed review of this supplemental application as submitted with draft labeling. In order to furnish adequate information for the safe use of the drug, the following revisions in the labeling should be made:

A. DESCRIPTION:

The structural formula of the drug should preceed the text material in this section.

B. INDICATIONS:

The last line of number 9 in this section should be rephrased to read "reduced amounts of meperidine or other narcotic as an adjunct to anesthesia and analgesia."

C. CONTRAINDICATIONS:

1. In the first paragraph the word "and" following the statements in parentheses should be deleted, a comma inserted and the following phrase added, "in patients who have bone marrow depression" so that the paragraph will now read as follows "Promethazine is contraindicated in comatose states, in patients who have received large amounts of central nervous system

depressants (alcohol, barbiturates, narcotics, etc.), in patients who have bone marrow depression and in patients who have demonstrated an idiosyncrasy or hypersensitivity to promethazine."

2. Since arterial injection is not an acceptable means of administering drugs, the second paragraph should be deleted.

D. WARNINGS:

1. In the paragraph entitled "Usage in Pregnancy," the following sentence should be added: "Jaundice and hyperreflexia have been reported in infants whose mothers received phenothiazines during pregnancy."

2. In the paragraph entitled "USAGE IN CHILDREN," the following sentence should be added: "Promethazine or any phenothiazine, used for symptomatic relief of nausea and vomiting associated with viral diseases, may mask early signs of developing central nervous system involvement, such as Reye's Syndrome."

3. The paragraph entitled "USE IN THE ELDERLY" should be modified by adding the following statement as a second sentence: "Because of reduced therapeutic requirements, dosage should be reduced accordingly."

4. After the "USE IN THE ELDERLY" paragraph, insert the following paragraph: "Promethazine should be used with extreme caution in patients with:

asthmatic attack

narrow angle glaucoma
prostatic hypertrophy
stenosing peptic ulcer
pyloroduodenal obstruction
bladder neck obstruction
patients receiving monoamine oxidase inhibitors"

5. The last paragraph as it appears on page three of the draft labeling should be modified as follows: the statement "when used intravenously, promethazine hydrochloride should be given in a concentration no greater than 25 mg per cc, and at a rate not to exceed 25 mg per minute," should be deleted and removed to the DOSAGE AND ADMINISTRATION section. Preceeding the remainder of the paragraph the following statement should appear, all in caps: "ASPIRATION OF DARK BLOOD DOES NOT PRECLUDE INTRA-ARTERIAL NEEDLE PLACEMENT AS BLOOD IS DISCOLORED UPON CONTACT WITH PROMETHAZINE." The remainder of the paragraph is acceptable.

E. PRECAUTIONS:

1. In the first paragraph, 4th line, the word "by" should be changed to "to" so that the sentence will read: "The dose of a narcotic or a barbiturate should be reduced to 1/4 to 1/2 the usual amount when promethazine is administered concomitantly."

2. The following phrase should be added to the second paragraph: "or those with a history of ulcer disease."

3. The following paragraphs should be added to this section:

"Promethazine can block and even reverse some of the actions of epinephrine."

"Promethazine should be used cautiously in persons with acute or chronic respiratory impairment, particularly children. The cough reflex may be suppressed. Drying effects may result in inspisation of secretions in lower respiratory disease."

F. ADVERSE REACTIONS:

1. Prior to the paragraph entitled "CNS Effects," the following statements should appear: "Pharmacological similarities among the phenothiazine derivatives requires consideration when promethazine is administered. There have been occasional reports of sudden death in patients receiving phenothiazine derivatives chronically."

2. The paragraph entitled "Cardiovascular Effects" should be revised. This paragraph should be rewritten as follows: "Postural hypotension is the most common cardiovascular effect of promethazine. Reflex tachycardia associated with mild increases in blood pressure have been seen with the use of promethazine hydrochloride. Bradycardia, faintness, dizziness and EKG changes, including blunting of T waves and prolongation of the Q-T INTERVAL may be seen. INTERARTERIAL INJECTION MAY RESULT IN GANGRENE OF THE AFFECTED EXTREMITY."

3. The paragraph entitled "Gastrointestinal" should be modified to read: "Anorexia, nausea, vomiting, epigastric distress, constipation, diarrhea and dry mouth have been reported."

4. Insert the following paragraph: "Genitourinary: Urinary frequency, dysurea and urinary retention may occur."

5. In the paragraph entitled "Allergic Reactions," delete the phrase, "at the injection site" so that the sentence will now read: "These include urticaria, dermatitis, asthma, and photosensitivity." The second sentence should read as follows: "Edematous reactions, such as laryngeal edema, angiodema and anaphylactoid reactions may occur."

6. The section entitled "Paradoxical Reaction" should be modified to read as follows: "Hyperexcitability and abnormal movements have been reported in children as manifestations of central nervous system toxicity following a single dose of 25 to 50 mg of promethazine hydrochloride. Nightmares and psychotic behavior have also been reported. Improper management of the central nervous system toxicity may result in respiratory and central nervous system depression."

7. Following the ADVERSE REACTIONS section, insert another section which is to be entitled "DRUG INTERACTIONS: MAO INHIBITORS AND THIAZIDE DIURETICS PROLONG AND INTEN-

SIFY THE ANTICHOLINERGIC EFFECTS OF PROMETHAZINE. Combined use of MAO inhibitors and promethazine may result in hypertension and extrapyramidal reactions."

"Narcotics—the CNS depressant and analgesic effects of narcotics are potentiated by phenothiazines (See WARNINGS)."

"The following drugs may result in potentiation of phenothiazine effects:

Oral Contraceptives
Progesterone
Reserpine
Nylidrin Hydrochloride"

G. DOSAGE AND ADMINISTRATION:

1. Under "DOSAGE AND ADMINISTRATION" following the first paragraph, insert the sentence, "When used intravenously, promethazine hydrochloride should be given in a concentration no greater than 25 mg/ml at a rate not to exceed 25 mg per minute."

2. In the paragraph entitled "Sedation," insert the word "adult" between the words "hospitalized" and "patient" so that the paragraph will read as follows: "In hospitalized adult patients, nighttime sedation may be achieved by a dose of 25 to 50 mg of promethazine hydrochloride."

3. In the paragraph entitled "Obstetrics," at the end of the paragraph insert the phrase "not to exceed 75 mg in any 8 hour period, or a total of 100 mg in any 24 hour period."

4. In the paragraph entitled "Children," add the following statement: "Promethazine should not be used for antiemetic effect in vomiting of unknown etiology in children (See WARNINGS)."

H. MANAGEMENT OF OVERDOSAGE:

In the second paragraph following the third sentence, insert this sentence, "Extrapyramidal symptoms may be treated with antiparkinson drugs such as barbiturates or diphenhydramine hydrochloride." The remainder of the paragraph is acceptable.

I. HOW SUPPLIED:

A HOW SUPPLIED section must be included in the package insert.

Please submit your revised labeling in draft form for our review.

Sincerely yours,

/s/

Margaret A. Clark, M.D.
Director
Division of Surgical-
Dental Drug Products
Bureau of Drugs

MINUTES OF ADVISORY COMMITTEE MEETING HELD OCTOBER 14, 1976 (DEFENDANT'S TRIAL EXHIBIT S)

FOOD AND DRUG ADMINISTRATION
BUREAU OF DRUGS
ANESTHESIOLOGY ADVISORY COMMITTEE
EIGHTEENTH MEETING

October 14, 1976

Teakwood Suite
The San Francisco Hilton
Mason and O'Farrell Streets
San Francisco, California

MEMBERS OF THE ADVISORY COMMITTEE PRESENT:

Betty J. Bamforth, M.D.—Chairman
Philip R. Bromage, M.B.
Burnell R. Brown, Jr., M.D., Ph. D.
Helmut F. Cascorbi, M.D., Ph. D.
Athole G. Jacobi, M.D.
Kenneth Sugioka, M.D.

MEMBERS OF THE ADVISORY COMMITTEE ABSENT:

M. Robert Knapp, M.D.

BUREAU OF DRUGS PERSONNEL IN ATTENDANCE:

Gerald M. Rachanow, Executive Secretary
Margaret A. Clark, M.D., HFD-160
Patricia H. Russell, M.D., HFD-160
David L. Scally, M.D., HFD-160

PUBLIC ATTENDEES:

Jeffrey M. Baden—Stanford, California
Harold H. Borgstodt, M.D.—Rochester, New York
Terrell A. Crowley, Ph.D.—North Chicago, Illinois
Edmond I. Eger, II, M.D.—San Francisco, California
Louis L. Ferstandig, Ph.D.—Hackensack, New Jersey

Ben Hitt, Ph.D.—Stanford, California
Duncan A. Holaday, M.D.—Miami, Florida
John B. Jewell, M.D.—New York, New York
Richard I. Mazze, M.D.—Stanford, California
James L. McMahon—New York, New York
William A. Mischel—Lexington, Massachusetts
W. D. Northcroft—San Mateo, California
James L. Ryan—Santa Ana, California
Charles W. Simons—Lexington, Massachusetts
Bradley E. Smith, M.D.—Nashville, Tennessee
Ross C. Terrell—New Providence, New Jersey
James F. Vitcha—Cape Coral, Florida

ANESTHESIOLOGY ADVISORY COMMITTEE

The meeting was called to order at 9:00 A.M., Dr. Betty J. Bamforth, Chairman, presiding. Dr. Athole G. Jacobi, the newest Committee member, was introduced.

OPEN PUBLIC HEARING:

An opportunity was provided for members of the public present to make comments or ask questions relevant to the Advisory Committee's agenda or other work, and no comments or questions were presented.

OPEN COMMITTEE DISCUSSION:

The first item on the agenda was a short presentation by the Executive Secretary concerning recent changes in FDA advisory committee procedures.

* * *

The second item on the agenda was the proposed package insert revision for Phenergan (promethazine hydrochloride) Injection, NDA 8-857, The FDA has proposed that the first paragraph of the CONTRAINDICATIONS section of the package insert be revised to state: "Promethazine is contraindicated in comatose states, in patients who have received large amounts of

central nervous system depressants (alcohol, barbiturates, narcotics, etc.), in patients who have bone marrow depression, and in patients who have demonstrated an idiosyncrasy or hypersensitivity to promethazine." The manufacturer, Wyeth Laboratories, disagrees with the contraindication to the use of Phenergan Injection in bone marrow depression. The question presented to the Advisory Committee was whether "Based on the limited case reports of blood dyscrasias which have been received, should the use of Phenergan Injection be contraindicated in bone marrow depression? or would a WARNING statement be more appropriate at this time?" The Committee agreed that present evidence does not warrant a contraindication, but that it certainly warrants a warning.

The FDA medical officer had suggested that since arterial injection is not an acceptable means of administering drugs that the second paragraph of the CONTRAINDICATIONS section (concerning intra-arterial injection) be deleted. Wyeth Laboratories has stated its strong feeling that this contraindication to the intra-arterial injection of Phenergan is entirely appropriate in its present location and is essential to ensure the safe use of this drug. The question presented to the Advisory Committee was "Should the reference to intra-arterial injection remain or be deleted from the CONTRAINDICATIONS section?" The Committee agreed that it had no objections to including this statement under CONTRAINDICATIONS and that, because of the seriousness of the problem, statements concerning intra arterial injection which appear in the WARNINGS section should remain there also.

One of the Committee members commented that the present statement (i.e., Subcutaneous injection is not recommended; ...) concerning subcutaneous injection

was pretty mild and that this statement should be made stronger or should appear in the CONTRAINDICATIONS section because there have been at least three or four cases of abscesses developing because of subcutaneous injection of the drug. He added that tissue necrosis and slough may follow subcutaneous injection and that the drug should be given by deep intra-muscular injection. The Committee agreed that an additional paragraph should be added to the CONTRAINDICATIONS section stating that Phenergan Injection should not be given by subcutaneous injection (because of the possibility of abscesses developing and of tissue necrosis) and that deep intra-muscular injection is the recommended route of administration of the drug.

The FDA medical officer had suggested that under the WARNINGS section of the package insert in the paragraph entitled Usage in Pregnancy that the following sentence be added: "Jaundice and hyperreflexia have been reported in infants whose mothers received phenothiazines during pregnancy." A number of literature references had been provided to Committee members and the question presented to the Committee was "Do you feel that sufficient evidence exists to require a statement about jaundice and hyperreflexia in infants of mothers receiving phenothiazines in labor?" The Committee and the FDA medical officer agreed that this statement could not be substantiated via the literature and should not be included in this section of the package insert.

Under the WARNINGS subsection entitled Use in the Elderly (approximately 60 years or older) the FDA has suggested the following statement be added as a second sentence "Because of reduced therapeutic requirements, dosage should be reduced accordingly." Wyeth Laboratories disagrees with a reduced therapeutic re-

quirement for Phenergan in elderly patients. The question presented to the Advisory Committee was "Do you agree with the statement that therapeutic requirements are, in general, decreased in elderly patients, and if so, that the Phenergan Injection package insert should contain such a statement?" The Committee agreed that a generic statement informing that "Since therapeutic requirements for sedative drugs tend to be lees in elderly patients, the dosage of Phenergan should be reduced for these patients." should be added to this section of the package insert.

The next question presented to the Advisory Committee was "Should information concerning the potentiation of toxicity of local anesthetics described in the article from Dental Abstracts (April 1975, pp. 238-239) be incorporated into the WARNINGS section of the package insert?" The Committee agreed that there does not currently appear to be any great difficulty associated with the combination of local anesthetics and promethazine, and that there is no reason for including any such warning in the package insert.

It was noted that Phenergan is frequently used in combination with narcotic and more potent anticholinergic agents such as scopolamine and atropine. The question presented to the Advisory Committee was "Would it be appropriate for the package insert to contain a statement (in the PRECAUTIONS section) cautioning against cough suppression and inspissation of secretions in lower respiratory tract disease?" The Committee agreed that this is too small a problem to put in the PRECAUTIONS section of the package insert.

The Committee was asked whether the following or a similar statement should appear in the ADVERSE REACTIONS section of the package insert: "Pharma-

cological similarities among the phenothiazine derivatives requires consideration when Phenergan is administered. There have been occasional reports of sudden death in patients receiving phenothiazine derivatives chronically." or would this type of statement be more appropriate under the "DRUG INTERACTIONS" section of the package insert? The Committee agreed that the statement as made does not imply a drug interaction and should not be included in this section of the package insert. The Committee agreed that a generic statement common to all phenothiazines should be included in the ADVERSE REACTIONS section, e.g., that sudden death has been reported following chronic therapy with these drugs.

The FDA has proposed that the subsection entitled "Paradoxical Reaction" be modified to read as follows: "Hyperexcitability and abnormal movements have been reported in children as manifestations of central nervous system toxicity following a single dose of 25 to 50 mg. of promethazine hydrochloride. Nightmares and psychotic behavior have also been reported. Improper management of the central nervous system toxicity may result in respiratory and central nervous system depression." The manufacturer has responded that the reference to central nervous system "toxicity" of promethazine is misleading and that the term "toxicity" is inappropriately used; also that the sentence referring to "improper management of the central nervous system toxicity is misleading and that it is not clear what information this sentence is trying to convey." The questions presented to the Committee were (1) Do you agree that paradoxical reactions are, in fact, evidence of CNS toxicity of promethazine and should be so identified to avert further dosing to "control" the reaction? and (2) Do the suggested sentences convey this infor-

mation? If not, how should this section be revised to convey this information? The FDA medical officer clarified the reasoning for proposing the word "toxicity," e.g., if you call it a toxic reaction, then the physician will not give more promethazine in an attempt to control the abnormal reaction which has occurred. The Committee agreed that the reaction need not be classified as a "toxicity" and that it is more important that the package insert state that the drug should be discontinued if such a reaction occurs. The Committee agreed that the following information should be stated in the package insert: "Hyperexcitability and abnormal movements which have been reported in children following a single administration of promethazine may be manifestations of relative overdosage, in which case consideration should be given to the discontinuation of the promethazine and to the use of other drugs." The Committee further stated that the name of the subsection should be changed from "Paradoxical Reaction" to "Overdosage."

Under DOSAGE AND ADMINISTRATION, the following question was presented to the Committee: "Based on knowledge that Phenergan crosses the placental barrier within 90 seconds and may reach 95% of maternal concentration in cord blood (Fisher, D. E. and J. B. Paton 'The Effect of Maternal Anesthetic and Analgesic Drugs on the Fetus and Newborn,' Clin. Obstet. Gynecol. 17, 275-287, June 1974), would suggested dosage limits of 75 mg. in any eight hour period and 100 mg. in 24 hours be appropriate in the OBSTETRICS subsection of the DOSAGE AND ADMINISTRATION section? (The manufacturer's recommended pediatric dosage is 0.5 mg./lb. or approximately 3.5 mg. for a seven lb. baby.)" The Committee agreed that 100 mg.

is a reasonable and sound recommendation for maximum obstetrical dosage during a 24-hour period.

The Committee was also asked: "Since it appears that it may be difficult to aspirate or be aware of intra-arterial pressure when using Wyeth's Tubex system to administer this drug and that more intra-arterial injections occur when the Tubex system is used is used in place of a plain needle and syringe, should the use of Tubex be discussed in this section (or perhaps in the PRECAUTIONS section)?" The Committee agreed that the following statement should be added under the Parenteral Administration subsection of the WARNINGS section: "If a Tubex system is used for intravenous injection, the drug should be injected into a satisfactorily functioning intravenous set."

The following general question was presented to the Committee: "In view of the fact that a physician may prescribe any of the Phenergan dosage forms for premedication or sedation, would a single package insert for all Phenergan dosage forms (excluding the expectorant combinations) be appropriate? or would a separate package insert for the injection be more appropriate in view of the following statement which appears in the current package insert, e.g., 'The injectable form of promethazine hydrochloride is indicated for the following conditions when use of the oral form is impractical'?" Committee members felt that the CNS effects described in pediatric patients were more likely to occur in a clinical situation with the oral dosage form rather than the injectable form. The committee agreed that a single package insert for all Phenergan dosage forms (excluding the expectorant combinations) would be more appropriate than separate inserts.

One Committee member noted that there have been reports of deep vein thromboses due to intravenous injections made in the lower leg. Another Committee member mentioned that Phenergan should also not be injected into a small hand vein because of the limited blood circulation. The Committee agreed that a generic statement could be added to the package insert that deep vein thromboses occur more commonly when drugs are injected into the lower extremities. One Committee member suggested an editorial change, e.g., where the package insert uses the word agent(s), this should be changed to the word drug(s).

The third item on the agenda was a discussion of the comments received to the Federal Register proposed rule (41 FR 14883, April 8, 1976) regarding "Requirements for Inhalation Anesthetic Drug Products—Studies for Carcinogenic and Teratogenic Potential."

* * *

This concluded the open portion of the meeting.

CLOSED PRESENTATION OF DATA:

A new protocol for Phase 1 studies under IND 12,639 was discussed. Representatives of the sponsor of IND 11,551 and their clinical investigators were present to discuss the preclinical and Phase 1 studies of this drug.

CLOSED COMMITTEE DELIBERATIONS:

Specific questions were presented concerning the protocol for IND 12,639 and the studies conducted under IND 11,551, and a number of recommendations were made concerning the investigation of these drugs.

The next meeting was tentatively scheduled for March 1977.

The meeting adjourned at 2:45 P.M.

I certify that I attended the eighteenth meeting of the Anesthesiology Advisory Committee of the Food and Drug Administration on October 14, 1976, and that these minutes accurately reflect what transpired.

Chairman /s/
Betty J. Bamforth, M.D.

Executive Secretary /s/
Gerald M. Rachanow

LETTER FROM WYETH TO FDA DATED SEPTEMBER 21, 1981 (DEFENDANT'S TRIAL EXHIBIT T)

WYETH LABORATORIES INC. [logo] *Box 8299, Philadelphia, Pennsylvania, 19101*
(215) 688-4400

REGULATORY AFFAIRS

September 21, 1981

NDA 8-857

James P. Mann, M.D., Director
Division of Surgical-Dental Drug Products
Food and Drug Administration
Bureau of Drugs
5600 Fishers Lane
Rockville, Maryland 20857

Dear Doctor Mann:

Reference is made to our approved NDA No. 8-857 for "Phenergan®, promethazine hydrochloride, Injection" and to the Federal Register Notices of June 26, 1979 and May 16, 1980 relating to Format and Content of Physician Labeling.

We are pleased to provide herewith draft copy of the package inserts for this product revised to conform to the requirements contained in the Federal Register Notice of June 26, 1979.

Sincerely yours,

WYETH LABORATORIES INC.

Paul V. Uses

Manager, Drug Regulatory Affairs Section

PVU:reb
Encs.

bcc: Dr. Agersborg
Mr. Barry
Mr. Bathish
Mr. Golden
Dr. Gold
Dr. Lewis w/atts.
Mr. Ross
Dr. Shaw w/atts.
Mr. Spitznagel w/atts.

THIS BLOCK FOR PRODUCT [illegible]

WYETH LABORATORIES REQUEST FOR REVISED PRODUCT SPECIFICATION REFERENCE GEN MGMT STANDARD PROCEDURE [illegible]	SUBMIT SINGLE COPY TO DIRECTOR OF THE PROJECT COORDINATION DIV., [illegible]	[illegible]
PRODUCT NAME Phenergan® (promethazine HCl) Injection		PRODUCT AND/OR PACKAGE NO.
REQUEST TO CHANGE EXISTING SPECIFICATION FOR: ☐ FORMULA (NO CHANGE IN PRODUCT NO.) ☐ MANUFACTURING DIRECTIONS ☐ TESTING STANDARDS ☒ LABELING ☐ [illegible]		

DETAILED DESCRIPTION OF REQUEST (ATTACH MARKED-UP COPY OF CURRENT SPECIFICATION WHEN APPROPRIATE)
Attached.

REASON FOR REQUEST
The attached direction circular has been revised in accordance with FDA Guidelines published in the Federal Register for June 25, 1979, and in keeping with the schedule mandated in the Federal Register, Volume 45, No. 97, Friday, May 16, 1980. As stipulated in the latter publication, this draft labeling is to be submitted for FDA review and approval before being put into use; no labeling changes, therefore, are to be made at this time.

SUBMITTED BY		DATE SUBMITTED	[illegible]
/s/ Earl T. Lewis, M.D. /	/s/ Daniel L. Shaw, Jr., M.D.	9/18/81	3/1/82
APPROVAL TO BEGIN WORK ON [illegible]		DATE APPROVED	TARGET DATE FOR REVISED [illegible]

WYETH A.H.F.S. CATEGORY 4:00, 28:24, 56:20

PHENERGAN®

(promethazine HCL)

INJECTION

* * *

CONTRAINDICATIONS

Promethazine is contraindicated in comatose states, in patients who have received large amounts of central-nervous-system depressants (alcohol, barbiturates, narcotics, etc.) and in patients who have demonstrated an idiosyncrasy or hypersensitivity to promethazine.

Under no circumstances should promethazine be given by intra-arterial injection due to the likelihood of severe arteriospasm and the possibility of resultant gangrene (see Warnings).

Phenergan injection should not be given by the subcutaneous route; evidence of chemical irritation has been noted and necrotic lesions have resulted on rare occasions following subcutaneous injection. The preferred parenteral route of administration is by deep intramuscular injection.

WARNINGS

Promethazine may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a vehicle or operating machinery. The concomitant use of alcohol or other central-nervous-system depressants may have an additive effect (see Precautions—"Drug Interactions"). Patients should be warned accordingly.

Inadvertent Intra-Arterial Injection

Due to the close proximity of arteries and veins in the areas most commonly used for intravenous injection, extreme care should be exercised to avoid perivascular extravasation or inadvertent intra-arterial injection. Reports compatible with inadvertent intra-arterial injec-

tion of promethazine, usually in conjunction with other drugs intended for intravenous use, suggest that pain, severe chemical irritation, severe spasm of distal vessels, and resultant gangrene requiring amputation are likely under such circumstances. Intravenous injection was intended in all the cases reported but perivascular extravasation or arterial placement of the needle is now suspect. There is no proven successful management of this condition after it occurs, although sympathetic block and heparinization are commonly employed during the acute management because of the results of animal experiments with other known arteriolar irritants.

Aspiration of dark blood does not preclude intra-arterial needle placement, because blood is discolored upon contact with promethazine. Use of syringes with rigid plungers or of small bore needles might obscure typical arterial backflow if this is relied upon alone.

When used intravenously promethazine hydrochloride should be given in a concentration no greater than 25 mg. per ml. and at a rate not to exceed 25 mg. per minute. When administering any irritant drug intravenously it is usually preferable to inject it through the tubing of an intravenous infusion set that is known to be functioning satisfactorily. In the event that a patient complains of pain during intended intravenous injection of promethazine, the injection should immediately be stopped to provide for evaluation of possible arterial placement or perivascular extravasation.

Injection into or near a nerve may result in permanent tissue damage.

Use in Children

Excessively large dosages of antihistamines, including promethazine, in children may cause hallucinations,

convulsions, and sudden death (see Adverse Reactions—"Paradoxical Reactions"). In children who are acutely ill associated with dehydration, there is an increased susceptibility to dystonias with the use of injectable antihistamine CAUTION SHOULD BE EXERCISED WHEN ADMINISTERING PHENERGAN TO CHILDREN. ANTIEMETICS ARE NOT RECOMMENDED FOR TREATMENT OF UNCOMPLICATED VOMITING IN CHILDREN, AND THEIR USE SHOULD BE LIMITED TO PROLONGED VOMITING OF KNOWN ETIOLOGY. THE EXTRAPYRAMIDAL SYMPTOMS WHICH CAN OCCUR SECONDARY TO PHENERGAN® ADMINISTRATION MAY BE CONFUSED WITH THE CNS SIGNS OF UNDIAGNOSED PRIMARY DISEASE, e.g., ENCEPHALOPATHY OR REYE'S SYNDROME. THE USE OF PHENERGAN SHOULD BE AVOIDED IN CHILDREN WHOSE SIGNS AND SYMPTOMS MAY SUGGEST REYE'S SYNDROME, OR OTHER HEPATIC DISEASES.

* * *

ADVERSE REACTIONS

CNS EFFECTS:

Drowsiness is the most prominent CNS effect of this drug. Extrapyramidal reactions may occur with high doses; this is almost always responsive to a reduction in dosage. Other reported reactions include dizziness, lassitude, tinnitus, euphoria, diplopia, nervousness, insomnia, tremors, convulsive seizures, oculogyric crises, excitation, catatonic-like states, and hysteria.

CARDIOVASCULAR EFFECTS:

Tachycardia, bradycardia, faintness, dizziness, and increases and decreases in blood pressure have been re-

ported following the use of promethazine hydrochloride injection. Venous thrombosis at the injection site has been reported. INTRA-ARTERIAL INJECTION MAY RESULT IN GANGRENE OF THE AFFECTED EXTREMITY (see Warnings).

GASTROINTESTINAL:

Nausea and vomiting have been reported, usually in association with surgical procedures and combination drug therapy.

ALLERGIC REACTIONS:

These include urticaria, dermatitis, asthma, and photosensitivity. Occurrence of photosensitivity may be a contraindication to further treatment with promethazine or related drugs. Angioneurotic edema has been reported.

OTHER REPORTED REACTIONS:

Thrombocytopenic purpura and jaundice of the obstructive type have been associated with the use of promethazine. The jaundice is usually reversible on discontinuation of the drug. Subcutaneous injection has resulted in tissue necrosis. Nasal stuffiness may occur. Patients may occasionally complain of autonomic reactions such as dryness of the mouth and blurring of vision.

PARADOXICAL REACTIONS (OVERDOSAGE):

Hyperexcitability and abnormal movements which have been reported in children following a single administration of promethazine may be manifestations of relative over-dosage, in which case, consideration should be given to the discontinuation of the promethazine and to the use of other drugs. Respiratory depression, nightmares, delirium, and agitated behavior have also been reported in some of these patients.

* * *

DOSAGE AND ADMINISTRATION

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

Do not use Phenergan if solution is discolored or contains a precipitate.

To avoid the possibility of physical and/or chemical incompatibility, consult specialized literature before diluting with any injectable solution or combining with any other medication. Do not use if there is a precipitate or any sign of incompatibility.

Important Notes on Administration

The preferred parenteral route of administration for promethazine hydrochloride is by deep intramuscular injection. The proper intravenous administration of this product is well-tolerated, but use of this route is not without some hazard.

INADVERTENT INTRA-ARTERIAL INJECTION CAN RESULT IN GANGRENE OF THE AFFECTED EXTREMITY (see Warnings). SUBCUTANEOUS INJECTION IS CONTRAINDICATED AS IT MAY RESULT IN TISSUE NECROSIS (see Contraindications).

Injection into or near a nerve may result in permanent tissue damage.

When used intravenously, promethazine hydrochloride should be given in concentration no greater than 25 mg/ml at a rate not to exceed 25 mg. per minute; it is preferable to inject through the tubing of an intravenous infusion set that is known to be functioning satisfactorily.

ALLERGIC CONDITIONS:

The average adult dose is 25 mg. This dose may be repeated within two hours if necessary, but continued therapy, if indicated, should be via the oral route as soon as existing circumstances permit. After initiation of treatment, dosage should be adjusted to the smallest amount adequate to relieve symptoms. The average adult dose for amelioration of allergic reactions to blood or plasma is 25 mg.

SEDATION:

In hospitalized adult patients, nighttime sedation may be achieved by a dose of 25 to 50 mg. of promethazine hydrochloride.

PRE- AND POST-OPERATIVE USE:

As an adjunct to pre- or post-operative medication, 25 to 50 mg. of promethazine hydrochloride in adults may be combined with appropriately reduced doses of analgesics and atropine-like drugs as desired. Dosage of concomitant analgesic or hypnotic medication should be reduced accordingly.

NAUSEA AND VOMITING:

For control of nausea and vomiting the usual adult dose is 12.5 to 25 mg. not to be repeated more frequently than every four hours. When used for control of postoperative nausea and vomiting, the medication may be administered either intramuscularly or intravenously and dosage of analgesics and barbiturates reduced accordingly.

OBSTETRICS:

Phenergan in doses of 50 mg. will provide sedation and relieve apprehension in the early stages of labor. When labor is definitely established, 25 to 75 mg. (average dose, 50 mg.) promethazine hydrochloride may be given

intramuscularly or intravenously with an appropriately reduced dose of any desired narcotic. Amnesic agents may be administered as necessary. If necessary, Phenergan with a reduced dose of analgesic may be repeated once or twice at four-hour intervals in the course of a normal labor. A maximum total dose of 100 mg. of Phenergan may be administered during a 24-hour period to patients in labor.

CHILDREN:

In children under the age of 12 years the dosage should not exceed half that of the suggested adult dose. As an adjunct to premedication the suggested dose is 0.5 mg. per pound of body weight in combination with an equal dose of narcotic or barbiturate and the appropriate dose of an atropine-like drug. Antiemetics should not be used in vomiting of unknown etiology in children.

* * *

INTERNAL WYETH MEMORANDUM DATED MARCH 19, 1987 (PLAINTIFF'S SUMMARY JUDGMENT EXHIBIT 9)

[handwritten "File"]

INTERNAL CORRESPONDENCE

[logo]

to Dr. Earl Lewis	from James J. O'Shaughnessy
company WLI located Radnor A-2	company WLI located Radnor C-2
subject Phenergan® Injection Labeling Content and Format Evaluation by the FDA	date March 19, 1967

Dear Earl:

During a recent telephone conversation with Dr. David L. Scally of the FDA's Division of Surgical-Dental Drug Products, I learned that his Division plans to send a letter to Wyeth requesting extensive revisions in the text of the package insert for Phenergan Injection.

The letter from the FDA will address two supplemental applications filed with the Surgical-Dental Division—S-009, filed September 21, 1981 (draft copy) and S-012, filed November 13, 1986 (final printed labeling). Attached please find copies of the Wyeth letters covering both of the aforementioned submissions.

A proposed copy of the correspondence to be sent to Wyeth is currently being circulated within the Surgical-Dental Division, and the letter will be issued as

soon as all pertinent staff members provide their concurrence.

Dr. Scally agreed to provide the attached draft of his evaluation or our submissions, and the corresponding follow-up letter to be distributed to Wyeth. He does not expect the final versions of either document to vary significantly from his proposed copies. He indicated that the preeminent editorial change recommended in his communications is the incorporation of labeling relative to the recognition and management of unintended intraarterial injection.

The final letter from the FDA will solicit a response from Wyeth within 90 days. So, unless you have any objections to the recommendations provided by Dr. Scally, please make the necessary preliminary arrangements to provide for the revisions. I shall send you FDA's official correspondence as soon as it arrives.

Sincerely,

/s/

James J. O'Shaughnessy

JJO:dlo
25129

cc: Dr. Agersborg
Mr. Bathish
Dr. Canavan
Dr. Deith
Mr. Golden
Mrs. Ivester
Mr. Krieg
Dr. Richards
Dr. Rogers
Mr. Ross
Mr. Spitznagel
Dr. Walker
Regulatory Routing

LETTER FROM FDA TO WYETH DATED MARCH 26, 1987 (PLAINTIFF'S TRIAL EXHIBIT 47)

[logo]

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service

Food and Drug Administration
Rockville MD 20857

Stamp: MAR 26, 1987

NDA 8-857/S-009

Wyeth Laboratories
P.O. Box 8299
Philadelphia, PA 19101

Attention: Paul V. Uses
Associate Director
Drug Regulatory Affairs

Gentlemen:

Please refer to your supplemental new drug application dated September 21, 1981 (S-009) submitted pursuant to section 505(b) of the Federal Food, Drug and Cosmetic Act for Phenergan (promethazine HCl) Injection.

The supplemental application provides for revised labeling in conformance with the Labeling Format Revision Program (21 CFR 201.56 and 201.57).

Reference is also made to the agency letter dated November 5, 1984, requesting further revisions in the labeling. We have not yet received a response to the referenced letter. The following comments, most of which

were conveyed to you by Dr. D. Scally, should be incorporated in the revised labeling. Please note that the comments include some deficiencies which were noted in S-012 dated November 13, 1986, as well as those noted in the original labeling supplement dated September 21, 1981.

The labeling should be revised as follows:

DESCRIPTION

The DESCRIPTION section of the package insert should add the pH of the drug product as well as the molecular formula and weight of the drug substance.

CLINICAL PHARMACOLOGY

It is suggested that the first paragraph of this section be rephrased as follows:

> "Promethazine is a phenothiazine derivative, which differs structurally from the antipsychotic phenothiazines by the presence of a branched side chain and no ring substitution. It is thought that this configuration is responsible for its relative lack (1/10 that of chlorpromazine) of dopaminergic (CNS) action.
>
> "Promethazine is an H_1 receptor blocking agent. In addition to its antihistamine properties, it provides clinically useful sedative and antiemetic effects. In therapeutic dosages, promethazine produces no significant effects on the cardiovascular system."

CONTRAINDICATIONS

Please add the following statement to the CONTRAINDICATIONS section:

1. Conclude the first paragraph with: "... (hypersensitivity to promethazine) ... or other phenothiazines."

WARNINGS

Please revise your WARNINGS discussion of Inadvertent Intra-arterial Injection according to the following text:

"INADVERTENT INTRA-ARTERIAL INJECTION: There are reports of necrosis leading to gangrene, requiring amputation, following injection of promethazine, usually in conjunction with other drugs; the intravenous route was intended in these cases, but arterial or partial arterial placement of the needle is now suspect. The mechanism is uncertain, however, animal experiments with other arteriolar irritants suggest that the initiating factor may be platelet aggregation and thrombosis starting distal to the site of injection.

"The first sign may be the patient's reaction to a sensation of fiery burning, roughly following the distribution path of the injected artery; no more drug should be injected until the situation is remedied. Blanching may be present early, may be transient or may not be noted at all. Blotchy cyanosis and dark discoloration usually follows.

"There is no established treatment other than prevention:

1. Beware of the close proximity of arteries and veins at commonly used injection sites and consider the possibility of aberrant arteries.

2. When used intravenously, promethazine hydrochloride should be given in a concen-

tration no greater than 25 mg/ml and at a rate not to exceed 25 mg/minute. Injection through a properly running intravenous infusion may enhance the possibility of detecting arterial placement. In addition, this results in delivery of a lower concentration of any arteriolar irritant.

3. Subcutaneous swelling near the site of injection calls for discontinuation of promethazine administration and reevaluation of the situation. This sign may be indicative of venous extravasation, which may result in localized necrosis, or it may signify partial arterial placement of the needle or catheter.

4. Beware that the characteristic bright-red color of arterial blood is discolored by contact with promethazine. (Italics or different print underlined.)

"Post injury injection of vasodilators an/or arterial infusion of parenteral fluids are generally regarded as being of no value in altering outcome. Animal experiments and published individual case reports concerned with a variety of arteriolar irritants suggest that one or more of the following may be of benefit in reducing the area of necrosis:

1. Arterial injection of heparin at the site of injury, followed by systemic anticoagulation.

2. Sympathetic blood (or brachial plexus block in the arm), if anticoagulant therapy permits.

3. Intra-arterial glucocorticoid injection at the site of injury, followed by systemic steroids.

4. A recent case report (non-promethazine drug injury) suggests that intra-arterial urokinase may promote fibrinolysis, even if administered late in treatment."

The references supporting the above discussion are:

1. G.S.Buckspan, et.al., Intraarterial Drug Injury: Studies of Etiology and Potential Treatment, JL. SURG. RES. 24(4): 294-301, 1978.

2. M.P.Wiedeman, et. al., In Vivo Microscopic Observations of Intra-Arterial Injections of Barbiturates, JL. SURG. RES. 22(2): 94-108, 1977.

3. S.S.Brown, et. al., Intra-Arterial Barbiturates, BRIT. JL. ANAES. 40: 13-19, 1968.

4. J.S.Mathers & B. Goodhead, Intra-arterial Methohexitone and Thiopentone, ANAESTHESIA 21(1): 81-85, 1966.

5. G.A.Webb & N.Lampert, Accidental Arterial Injections, AM. J. OBST. & GYNEC. 101(3): 365-371, 1 June 1968.

6. H.S.Engler, et. al., Production of Gangrenous Extremities by Intra-Arterial Injections, AMERICAN SURGEON 30(9): 602-607, Sept. 1964.

7. D.L.Hager & J.N.Wilson, Gangrene of the Hand Following Intra-Arterial Injection, ARCH. SURG. 94: 86-89, Jan. 1967.

8. R.F.Lynas & W.I.K.Bisset, Intra-Arterial Thiopentone, ANAESTHESIA 24(2): 257-261, April 1969.

9. G.Corser, et. al., Ischaemia Following Self Administered Intra-Arterial Injection of Methylphenidate and Diamorphine, ANAESTHESIA 40: 51-54, 1985.

10. D.J.Waters, Intra-Arterial Thiopentone, ANAESTHESIA 21(3): 346-356, July 1966.

11. Correspondence Regarding Thiopental and Thiamylal (3 Letters): 1. L.C.Mark, 2. J.W.Dundee, 3. S.Dohi & H.Naito. ANESTHESIOLOGY 59: 153-155, 1983.

12. D.Albo, K.Reemtsma, et. al., Effect of Intra-Arterial Injections of Barbiturates, AMERICAN JL. OF SURGERY 120: 676-678, November 1970.

13. E.C.Klatte, et. al., Toxicity of Intra-Arterial Barbiturates and Tranquilizing Drugs, RADIOLOGY 92(4): 700-704, March 1969.

14. M.L.Nahrwold, et. al., Inadvertent Intra-Arterial Injection of Mephenteramine, ROCKY MOUNTAIN MEDICAL JOURNAL, 70(9): 38-39, September 1973.

15. G.Enloe, et. al., Hazards of Intra-Arterial Injection of Hydroxyzine, CANADIAN ANAES. SOC. JL. 16(5): 425-428, September 1969.

16. H.S.Engler, et. al., Gangrenous Extremities Resulting from Intra-Arterial Injections, ARCH. SURG. 94: 644-651, May 1967.

17. J.B.Kinmonth & R.C.Shepherd, Accidental Injection of Thiopentone Into Arteries, Studies of

Pathology and Treatment, BRITISH MEDICAL JOURNAL, 2: 914-918, 1959.

18. D.Goldsmith & N.Trieger, Accidental Intra-Arterial Injection: A Medical Emergency, ANESTHESIA PROGRESS 22(6): 180-183, Nov.-Dec. 1975.

19. R.Miller, et. al., Intra-Arterial Injection of a Barbiturate—A Case Report, ANESTHESIA PROGRESS 23(1): 25-27, Jan.-Feb. 1976.

20. H.H.Stone & C.C.Donnelly, REVIEW ARTICLE, The Accidental Intra-Arterial Injection of Thiopental, ANESTHESIOLOGY 22: 995-1006, 1961.

Please add the following statements to the WARNINGS section:

"Promethazine may lower seizure threshold. This should be taken into consideration when administering to persons with known seizure disorders or in combination with narcotics or local anesthetics which may also affect seizure threshold.

Promethazine has been associated with crib death and should be avoided in patients with a history of sleep apnea.

"Anticholinergic properties of promethazine have resulted in precipitation of acute narrow angle glaucoma, pyloroduodenal obstruction and urinary tract obstruction. Consideration should be given to the risk of these in prescribing promethazine for patients with a known predisposition to these complications such as those with stenosing peptic ulcer or benign prostatic hypertrophy.

"Administration of promethazine has been associated with reported cholestatic jaundice. This should be taken into consideration when interpreting laboratory results and when selecting medication in patients with impaired liver function.

"There are no data on safety or efficacy of use of promethazine injection to treat an acute asthmatic attack, therefore, such use is not recommended."

PRECAUTIONS

General

Please delete the first paragraph as this is now covered elsewhere ("Drugs having anticholinergic ... obstruction.")

Information for Patients

Please add the following paragraphs to this subsection:

"When appropriate, patients should be instructed to report any involuntary muscle movements or unusual sensitivity to light to their physician.

"When appropriate, it should be recommended that children be supervised to avoid potential harm in bike riding or other activities while their ability to react to hazardous situations is impaired.

Carcinogensis, Mutagensis, Impairment of Fertility

Revised labeling for carcinogensis, mutagensis, impairment of fertility and pregnancy is not supported by documented studies of promethazine concerning the Ames mutagensis study and rat teratology feeding study at doses of 6.25 and 12.5 mg/kg. These studies should be submitted to support the proposed labeling.

Pregnancy, Teratogenic Effects

As stated in your February 29, 1984, the statement "Specific studies to test the action of the drug on parturition, lactation, and development of the animal neonate were not done, but a general preliminary study in rats indicated no effect on these parameters," should be included.

Labor and Delivery

The discussion of Labor and Delivery (subsection of PRECAUTIONS) adds information to the effect that the drug is not apt to produce excessive sedation to mother or fetus when it is given as recommended, that the drug does not appreciably effect the duration of labor or delivery or the need for intervention or resuscitation in the process of delivery, and that there is no evidence that the drug if used during labor and delivery will have an effect on later growth, etc. No documentation is offered for any of these new claims.

The drug is approved for use in obstetrics, and this approval is not a subject of inquiry at this time. What is being questioned is the addition of unusual claims as to lack of side effects without submission of the data for review. These claims cannot he added to the prescription drug labeling until:

1. Satisfactory summaries, based upon adequate and well controlled studies, are submitted for review.
2. These studies are reviewed by our staff and you receive an "approvable" letter requesting the submission of final printed labeling.

In the event that these claims cannot be documented as specified above, this subsection of the

labeling shall state that the information is unknown (see 201.57(f)(7), page 37465 of the Federal Register Notice dated June 26, 1979).

Please also add to the following to the discussion of Labor and Delivery:

> "Promethazine administered during labor and delivery inhibits platelet aggregation (see nonteratogenic effects)."

OVERDOSAGE

The discussion of treatment of hypotension should begin by recommending that the treatment of choice is administration of intravenous fluids, accompanied by repositioning if indicated. The second sentence ("Severe hypotension—or phenylephrine") should be modified to read: "In the event that vasopressors are considered for the management of severe hypotension or hypotension which does not respond to intravenous fluids, etc., the administration of levarterenol or phenylephrine should be considered." Continue on with the third sentence and the rest of this section as contained in the September 21, 1981 submission.

DOSAGE & ADMINISTRATION

Please delete the sentence, under OBSTETRICS which reads: "Amnesic agents may be administered as necessary." There is no reason to single out this particular type of combined drug usage unless there is either substantial supporting data or significant drug interaction information. Perhaps this is a holdover from a previous era when amnesic agents were more popular with obstetricians.

HOW SUPPLIED

The following items should be included:

The HOW SUPPLIED section should also contain the storage temperature (range) based on stability data of the drug product. Although not mandatory, if an NDC number is added, it should be complete (e.g., NDC 0008-9142-01, lot#1860317, Tubex® Fast Trak® Syringe, 1 syringe of 2 ml size).

The text for the Direction for use should be identical. Please compare and contrast the final printed package insert number C13727-1 with C1 3477-1 issued March 29, 1985. The former is acceptable if the latter will be phased out.

Please submit revised draft labeling as soon as possible.

Sincerely yours,

/s/

Patricia H. Russell, M.D.
Acting Director
Division of Surgical-Dental
Drug Products
Office of Drug Research and
Review
Center for Drugs and Biologics

Stamp: RECEIVED
MAR 31 1987
DRUG REGULATORY AFFAIRS

INTERNAL WYETH MEMORANDUM DATED DECEMBER 1, 1987 (PLAINTIFF'S TRIAL EXHIBIT 46)

INTERNAL CORRESPONDENCE

[logo]

[handwriting: PVU
Pls. handle
[illegible 12/3]]

[illegible stamps and handwriting]

---

to List Below	from Earl T. Lewis, M.D. (initials)
company W-A located Radnor	company W-AR located Radnor
subject Labeling Changes for Phenergan® Injection Direction Circular	date December 1, 1987

Mr. Bathish
Dr. Deitch
Mr. Meaney
Dr. Walker
Mr. Ross

Attached is a proposed revision to the Phenergan Injection direction circular which deals specifically with the section on "INADVERTENT INTRAARTERIAL INJECTION" and is contained in the "WARNINGS" section. A change in this section has been requested by the FDA in several letters we have received this year

beginning with Dr. Russell's letter of March 26, 1987 to Mr. Paul Uses.

Also attached for your perusal and comparison are copies of the specific wording proposed by FDA as well as the section on Inadvertent Intraarterial Injection that is contained in our current Phenergan Injection direction circular.

Please review this proposed revision and make any comments or suggested changes on your copy and return it to me by Friday, December 11, 1987 so that final copy can be provided to the FDA within the time limits imposed.

Thank you for your assistance.

When preparing to give promethazine intravenously, extreme care should be exercised to avoid perivascular extravasation or inadvertent intra-arterial injection. There are reports of severe tissue injury, including necrosis with resultant gangrene requiring amputation, following the injection of promethazine, usually in conjunction with other drugs meant for intravenous use. Although the intravenous route was intended in all these cases arterial or partial arterial placement of the needle is now suspect. The mechanism of producing this injury is uncertain, however animal experiments with other arteriolar irritants suggest that the primary cause may be platelet aggregation and thrombosis starting distal to the site of injection.

The first indication of this problem is usually the patient's complaint of severe pain or sensation of fiery burning, roughly following the distribution path of the injected artery. At the first complaint of any pain during the intended intravenous injection of promethazine,

the injection should be stopped immediately and evaluated for possible arterial placement of the needle. Blanching may be present early, may be transient or may not be noted at all. Blotchy cyanosis and dark discoloration usually follow. Pain is usually persistent and the skin temperature distal to the injection site may be decreased.

There is no established treatment that has been shown to be successful in the management of this condition after it occurs. Post injury injection of vasodilators and/or arterial infusion of parenteral fluids are generally regarded as being of no value in altering outcome. Animal experiments and published individual case reports concerned with a variety of arteriolar irritants suggest that one or more of the following may be of benefit in reducing the area of necrosis:

1. Heparinization with continuous intra-arterial injection of heparin proximal to the site of injury until pain and swelling have subsided (up to two weeks).

2. Sympathetic block (or brachial plexus block in the arm), if anticoagulant therapy permits.

3. Intra-arterial glucocorticoid injection at the site of injury, followed by systemic steroids.

4. A recent case report (non-promethazine drug injury) suggests that intra-arterial urokinase may promote fibrinolysis, even if administered late in treatment.

Since prevention is the only method shown to be effective in dealing with this problem, the following points are among those that should be considered in its prophylaxis:

1. Beware of the close proximity of arteries and veins at commonly used injection sites and consider the possibility of aberrant arteries.

2. When used intravenously, promethazine hydrochloride should be given in a concentration no greater than 25 mg/ml and at rate not to exceed 25 mg/minute. Injection into an intravenous infusion set that is known to be running properly should decrease the possibility of inadvertently injecting promethazine intra-arterially. In addition, this results in delivery of a lower concentration of any arteriolar irritant.

3. Subcutaneous swelling near the site of injection calls for discontinuation of promethazine administration and reevaluation of the situation. This sign may be indicative of venous extravasation, which may result in localized necrosis, or it may signify partial arterial placement of the needle or catheter.

4. Be aware that the characteristic bright-red color of arterial blood is discolored by contact with promethazine (italics or different print underlined) so that the aspiration of dark blood does not preclude intra-arterial needle placement.

* * *

BEST AVAILABLE COPY

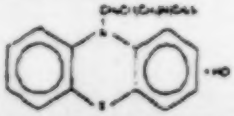
CI 2750-1 82.07

Wyeth®
Phenergan®
(promethazine HCl)
Injection

AHFS Category 4:00 28:24 56:20

Description

Phenergan HCl (10H-phenothiazine-10-ethanamine, N,N,α-trimethyl-, monohydrochloride) has the following structural formula:



Each mL of clear solutions under 25 mg or 50 mg promethazine hydrochloride with 0.1 mg sodium bisulfite, 0.91 mg calcium chloride, not more than 0.25 mg sodium metabisulfite and 5 mg phenol with sodium hydroxide/hydrochloric acid buffer.

Actions

Promethazine hydrochloride, a phenothiazine derivative, possesses both antihistaminic (blocking) and sedative properties. It is a competitive type of antihistamine which has been shown effective in the treatment of allergic conditions sensitive to such therapy, including the immediate hypersensitivity reactions to blood or plasma, various manifestations of the common cold, pruritic skin eruptions, and amelioration of reactions to insect bites and stings. Promethazine also has an antiemetic effect and is effective in the prevention and control of nausea and vomiting associated with surgical and obstetrical procedures. It potentiates the action of analgesics, thereby permitting reduction in dosage of these agents. Promethazine also has an anticholinergic effect and is a useful component of preanesthetic medication. It potentiates the action of barbiturates, narcotics, and other central nervous system depressants. Promethazine has a sedative effect in most patients, even in the presence of pain. Promethazine has an antitussive effect.

Indications

The injectable form of promethazine hydrochloride is indicated in the following conditions:

1. Prevention of allergic reactions to blood or plasma.
2. In preference to, or in addition to, epinephrine and other therapeutic measures after the acute symptoms have been controlled.
3. For other uncomplicated allergic conditions of the immediate type when oral therapy is impossible or contraindicated.
4. Active treatment of motion sickness.
5. Preoperative, postoperative, and obstetric (during labor) sedation.
6. Prevention and control of nausea and vomiting associated with certain types of anesthesia and surgery.
7. As an adjunct to analgesics for the control of postoperative pain.
8. For sedation and relief of apprehension and tension produced when used in small doses before operative procedures.
9. Intravenously, in special surgical situations, such as repeated anesthetic sessions during surgery and post-operative pain control, with reduced amounts of meperidine or other narcotic drug (prior to its second or subsequent administration).

Contraindications

Promethazine is contraindicated in premature infants, in patients who have received large amounts of central nervous system depressants (narcotic analgesics, antihistamines including barbiturates, general anesthetics, tranquilizers, sedatives, nonbarbiturate hypnotics, etc.) and in children who have demonstrated an idiosyncrasy or hypersensitivity to promethazine.

Lower-to-normal dosages should be given by the subcutaneous route, especially if intravenous use has been noted, and medical history does indicate an increased susceptibility to subcutaneous injection. The preferred parenteral route of administration is by deep intramuscular injection. The preferred parenteral route of administration is by deep intramuscular injection. The preferred parenteral route of administration is by deep intramuscular injection.

Warnings

Phenergan injection (drug) is [illegible] sodium metabisulfite, a sulfite that may cause allergic type reactions, including anaphylactic symptoms and life-threatening or less severe asthmatic episodes, in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in nonasthmatic people.

Promethazine may obscure the normal and/or physical signs required by the presence of pharmacologic incompatible liquids, such as drawing a vehicle or opening injection ampules. The administration use of sterile sodium hydroxide (including bacteriostatic sodium hydroxide, normal saline, sterile water, etc.) [illegible] may have an additive sedative effect. Patients should be advised accordingly.

USAGE IN PREGNANCY

The safe use of promethazine has not been established with regard to the possible adverse effects upon fetal development. The potential hazard for the use of this drug during pregnancy should be weighed against the possible benefit to the mother before giving this.

USE IN CHILDREN

Excessively large dosages of phenothiazines, including promethazine, in children may cause hyperpyrexia, convulsions, and sudden death. In children who are acutely ill, especially with dehydration, there is an increased susceptibility to dystonias with the use of promethazine hydrochloride injection.

CAUTION SHOULD BE EXERCISED WHEN ADMINISTERING PHENERGAN TO CHILDREN. ANTIEMETICS ARE NOT RECOMMENDED FOR TREATMENT OF UNCOMPLICATED VOMITING IN CHILDREN, AND THEIR USE SHOULD BE LIMITED TO PROLONGED VOMITING OF KNOWN ETIOLOGY. THE EXTRAPYRAMIDAL SYMPTOMS WHICH CAN OCCUR SECONDARY TO PHENERGAN ADMINISTRATION MAY BE CONFUSED WITH THE CNS SIGNS OF UNDIAGNOSED PRIMARY DISEASE, I.E., ENCEPHALOPATHY OR REYE'S SYNDROME. THE USE OF PHENERGAN SHOULD BE AVOIDED IN CHILDREN IN WHOSE SIGNS AND SYMPTOMS MAY SUGGEST REYE'S SYNDROME, OR OTHER HEPATIC DISEASES.

USE IN THE ELDERLY (APPROXIMATELY 60 YEARS OR OLDER)

Since the sedative requirements for sustaining drugs tend to be less in elderly patients, the dosage of Phenergan should be reduced or given [illegible].

OTHER CONSIDERATIONS

Drugs having anticholinergic properties should be used with caution in patients with asthmatic attack, narrow-angle glaucoma, prostatic hypertrophy, stenosing peptic ulcer, pyloroduodenal obstruction, and bladder neck obstruction.

Phenergan should be used with caution in patients with bone marrow depression. Leukopenia and agranulocytosis have been reported, usually when Phenergan has been used in association with other known toxic agents.

INADVERTENT INTRAARTERIAL INJECTION

Due to the close proximity of arteries and veins in the areas most commonly used for intravenous injection, extreme care should be exercised to avoid perivascular or intra-arterial injection of medication. Reports, sometimes with objective evidence of necrosis of [illegible] following intra-arterial injection of promethazine, usually in combination with other drugs irritating to arteries, have suggested that such severe effects may result from [illegible] and include gangrene requiring amputation. Such severe effects may result from [illegible] and include gangrene requiring amputation. Such severe effects may result from [illegible] and include gangrene requiring amputation.

Precautions

Promethazine may significantly affect the actions of other drugs. It may increase, prolong, or intensify the sedative action of central nervous system depressants, such as alcohol, sedatives (including barbiturates), tranquilizers, hypnotics, narcotics, narcotic analgesics, meperidine, etc. When given concomitantly with promethazine hydrochloride, the dose of barbiturates should be reduced by at least one-half, and the dose of narcotics should be reduced by one-quarter to one-half. Dosage must be individualized. Excessive amounts of promethazine may lead to restlessness and motor hyperactivity, in the absence of pain. These symptoms usually disappear with adequate control of the pain. Promethazine should be used cautiously in persons with cardiovascular disease or impairment of liver function.

Although neither of the recommended routes of administration has ever been reported with promethazine, the possibility should be considered in case of [illegible].

Adverse Reactions

CNS EFFECTS

Drowsiness is the most common CNS effect of promethazine. Confusion, [illegible] may occur with high doses. This is almost always responsive to reduction of dosage. Other reported reactions include [illegible], [illegible], [illegible],

LETTER FROM WYETH TO FDA DATED MAY 3, 1988 (DEFENDANT'S TRIAL EXHIBIT M)

RECEIPT COPY

WYETH-AYERST [logo] *LABORATORIES*

P.O. BOX 8299, PHILADELPHIA, PA 19101-1245 • *(215) 688-4400*

Division of American Home Products Corporation

U.S. REGULATORY AFFAIRS

Stamp: REC'D [Illegible]

May 3, 1988

NDA No. 8-857/S-009

Philip G. Walters, M.D., Acting Director
Division of Surgical-Dental Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Walters:

Reference is made to our approved new drug application no. 8-857 for "Phenergan®, promethazine hydrochloride, Injection" as well as to our September 21, 1981 (S-009) supplemental application, and subsequent amendments, providing package inserts revised to conform to the Federal Register notices relative to content and format labeling requirements for this product.

Reference is also made to your communications of May 26, 1987 and November 13, 1987 which requested additional changes in the text of the labeling covered by this supplemental application.

In response to your letters, we are pleased to provide herewith four draft copies of the revised Phenergan Injection package insert incorporating the changes recommended in your correspondence. Also, we have included additional medically significant information to the proposed text.

We trust that you will find this proposed labeling satisfactory and will so advise us at your earliest convenience.

Sincerely,

WYETH-AYERST LABORATORIES

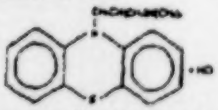
/s/

Paul V. Uses
Associate Director
Drug Regulatory Affairs

PVU:dlo
25352(4)

Wyeth®
Phenergan®
(promethazine HCl)
Injection

[redacted]



[redacted]

INSERT HERE:
Promethazine hydrochloride is a racemic compound; the empirical formula is $C_{17}H_{20}N_2S \cdot HCl$ and its molecular weight is 320.88. The pH for the drug product is between 4.0 and 5.5.

[redacted]

Clinical Pharmacology

DELETE THIS PARAGRAPH. SUBSTITUTE THE FOLLOWING:

Promethazine is a phenothiazine derivative, which differs structurally from the antipsychotic phenothiazines by the presence of a branched alkyl chain and no ring substitution. It is thought that this configuration is responsible for its relative lack (1/10 that of chlorpromazine) of dopaminergic (DA1) action.

Promethazine is an H1 receptor blocking agent. In addition to its antihistaminic properties, it exerted clinically useful sedative and antiemetic effects. In therapeutic dosages, promethazine produces no significant effects on the cardiovascular system.

Clinical effects are apparent within 15 to 20 minutes after intramuscular injection and within 3 to 5 minutes after intravenous injection; the duration of action is usually four to six hours, although effects may persist as long as 12 hours. Promethazine is metabolized by the liver to a variety of compounds; the sulfoxides of promethazine and N-demethylpromethazine are the predominant metabolites appearing in the urine.

[redacted]

and Usage

[redacted]

NDA-00005582

327

END PARAGRAPH WITH:
promethazine or other phenothiazines. .

ADD THE FOLLOWING WARNINGS:

Promethazine may lower seizure threshold. This should be taken into consideration when administering to persons with known seizure disorders or in combination with narcotics or local anesthetics which may also affect seizure threshold.

The anticholinergic properties of promethazine have resulted in precipitation of acute narrow angle glaucoma, pyloroduodenal obstruction and urinary tract obstruction. Although such conditions have been rare with promethazine, consideration should be given to the risk of these in prescribing promethazine, especially for patients with a known predisposition to these complications such as those with stenosing peptic ulcer or benign prostatic hypertrophy.

"There are no data on safety or efficacy of use of promethazine injection to treat an acute asthmatic attack, therefore, such use is not recommended."

"Administration of promethazine has been associated with reported cholestatic jaundice. This should be taken into consideration when interpreting laboratory results and when selecting medication in patients with impaired liver function.

DELETE THESE TWO PARAGRAPHS AND SUBSTITUTE THE INFORMATION FOUND ON THE NEXT PAGE

[redacted]

"se with caution in patients with lower respiratory disease, including asthma.

[redacted]

DELETE THESE FIVE LINES AND SUBSTITUTE THE INFORMATION FOUND DIRECTLY BELOW THEM

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

2.1 to 4.2

[redacted]

While antihistamines, including promethazine at a daily dosage level of 25 mg/kg intraperitoneally, have been found to produce fetal mortality in rodents, the pharmacological effects of histamine in the rodent do not parallel those in man.

[redacted] with respect to the possible adverse effect on fetal development. Therefore,

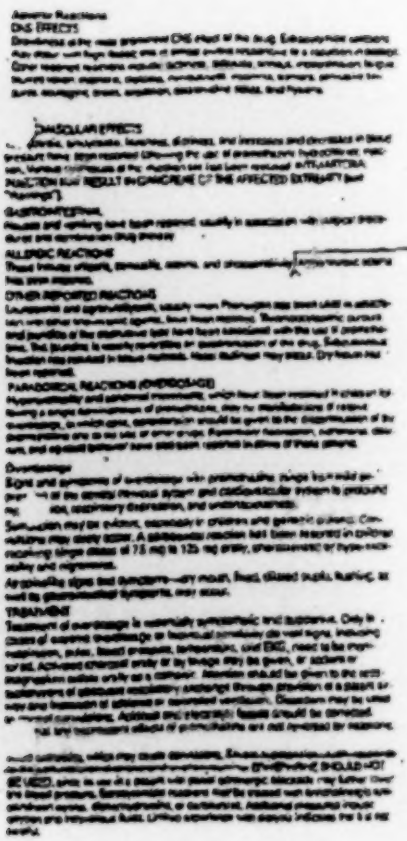
Promethazine administered during labor and delivery may inhibit platelet aggregation in the newborn. The clinical significance of this effect is unknown.

[redacted]

Limited data suggest that the use of Phenergan as a sedative during labor and delivery does not have an appreciable effect on the duration of labor or delivery or in increasing the chances that the newborn will require any type of intervention in the process of delivery when given as recommended. The effect on the later growth, development or functional maturation of the newborn when Phenergan has been used during labor and delivery is unknown.

[redacted]

[redacted]



INSERT HERE:
Occurrence of photosensitivity may be a contraindication to further treatment with promethazine or related drugs.

REPLACE THE SECOND SENTENCE WITH THE FOLLOWING:
The treatment of choice for resulting hypotension is administration of intravenous fluids, accompanied by repositioning if indicated. In the event that vasopressors are considered for the management of severe hypotension which does not respond to intravenous fluids and repositioning, the administration of levarterenol or phenylephrine should be considered.

[redacted] AND ADMINISTRATION

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

Do not use Phenergan [redacted] if solution is discolored or contains a precipitate.

To avoid the possibility of physical and/or chemical incompatibility, consult specialized literature before diluting with any injectable solution or combining with any other medication. Do not use if there is a precipitate or any sign of incompatibility.

Injection

Treatment Dosage and Administration

The preferred parenteral route of administration for promethazine hydrochloride is by deep intramuscular injection. The deep intramuscular administration of the product is well-established but use of this route is not without some hazard.

[redacted] INTRAARTERIAL INJECTION CAN RESULT IN GANGRENE OF THE AFFECTED EXTREMITY (see "Warnings"). SUBCUTANEOUS INJECTION IS CONTRAINDICATED, AS IT MAY RESULT IN TISSUE NECROSIS (see "Contraindications").

[redacted] ...within date or dose ... there may result in permanent tissue damage.

When used intravenously, promethazine hydrochloride should be given in concentrations no greater than 25 mg/mL, at a rate not to exceed 25 mg per minute (i.e. preferably by slowly passing the tubing of an intravenous infusion set that is known to be functioning satisfactorily).

ALL EMETIC CONDITIONS

The average adult dose is 25 mg. The dose may be repeated within two hours if necessary, but continued therapy, if indicated, should be with the oral route as soon as vomiting circumstances have ceased. After initiation of treatment, dosage should be adjusted to the smallest amount effective in relieving symptoms. The average adult dose for amelioration of emetic reactions in cases of pregnancy is 25 mg.

SEDATION

In management of adult patients, nighttime sedation may be achieved by a dose of 25 to 50 mg of promethazine hydrochloride.

PRE- AND POSTOPERATIVE USE

As an adjunct to 50% of barbiturate medication, 25 to 50 mg of promethazine hydrochloride in adults may be sufficient with somewhat reduced doses of concomitantly administered analgesic drugs as required. Dosage of concomitant analgesic or hypnotic medication should be reduced accordingly.

NAUSEA AND VOMITING

For control of nausea and vomiting, the usual adult dose is 12.5 to 25 mg, not to be repeated more frequently than every four hours. When used for control of postoperative nausea and vomiting, the medication may be administered either intramuscularly or slowly intravenously, and barbiturates reduced accordingly.

[redacted]

Promethazine in doses of 50 mg will provide sedation and relieve apprehension in the early stages of labor. When labor is sufficiently established, 25 to 75 mg (according to dose) of an analgesic/narcotic may be given intramuscularly or intravenously in combination with an agent of the phenothiazine class, such as promethazine hydrochloride, in reduced dosage. Administration of an analgesic/narcotic subsequently may be given in reduced dosage. Administration of an analgesic may be repeated once or twice at four-hour intervals in the absence of a specific labor pattern. A maximum total dose of 100 mg of Phenergan may be administered during a 24-hour period to patients in labor.

CHILDREN

In children under the age of 2 years, the dosage should not exceed half dose of the suggested adult dose. As an aid in arriving at the correct dose, the suggested dose of 0.5 mg per lb. of body weight of a child may be used. Administration of barbiturates and the appropriate dose of an antiemetic drug. Antiemetics should not be used in vomiting of unknown etiology in children.

DELETE THIS SENTENCE

ADD THE FOLLOWING SENTENCE AS THE FIRST PARAGRAPH UNDER THE SUBCATEGORY "CHILDREN":

Phenergan Injection should not be used in children less than 2 years of age.

(See Warnings).

How Supplied

[redacted] a products investigated as follows:

NDC 0008-0063-01, 25 mg per mL, 25 vials of 1 mL
NDC 0008-0077-01, 50 mg per mL, 25 vials of 1 mL

INSERT HERE:
Store at room temperature, approximately 25°C (77°F).

[redacted] AVAILABLE

[redacted] as follows:

NDC 0008-0416-01, 25 mg per mL, 25 TUBES of 1 mL
NDC 0008-0417-01, 50 mg per mL, 25 TUBES of 1 mL

[redacted] Laboratories Inc., Philadelphia PA 19101

[redacted]

333

NDA-00005588

LETTER FROM WYETH TO FDA DATED MAY 3, 1988 (DEFENDANT'S SUMMARY JUDGMENT EXHIBIT F)

RECEIPT COPY

WYETH-AYERST [logo] *LABORATORIES*

P.O. BOX 8299, PHILADELPHIA, PA 19101-1245 • *(215) 688-4400*

Division of American Home Products Corporation

U.S. REGULATORY AFFAIRS

Stamp: REC'D [Illegible]

May 3, 1988

NDA No. 8-857/S-009

Philip G. Walters, M.D., Acting Director
Division of Surgical-Dental Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Walters:

Reference is made to our approved new drug application no. 8-857 for "Phenergan®, promethazine hydrochloride, Injection" as well as to our September 21, 1981 (S-009) supplemental application, and subsequent amendments, providing package inserts revised to conform to the Federal Register notices relative to content and format labeling requirements for this product.

Reference is also made to your communications of May 26, 1987 and November 13, 1987 which requested additional changes in the text of the labeling covered by this supplemental application.

In response to your letters, we are pleased to provide herewith four draft copies of the revised Phenergan Injection package insert incorporating the changes recommended in your correspondence. Also, we have included additional medically significant information to the proposed text.

We trust that you will find this proposed labeling satisfactory and will so advise us at your earliest convenience.

Sincerely,

WYETH-AYERST LABORATORIES

/s/

Paul V. Uses
Associate Director
Drug Regulatory Affairs

PVU:dlo
25352(4)

WYETH-AYERST [logo] *LABORATORIES*

P.O. BOX 8299, PHILADELPHIA, PA 19101-1245 • *(215) 688-4400*

Division of American Home Products Corporation

August 22, 1988

Phenergan® Injection NDA No. 08-857/S-009

Amplification of Draft Labeling Submitted May 3, 1988

Phenergan® Injection NDA No. 08-857/S-009

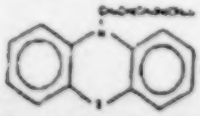
AMPLIFICATION OF DRAFT LABELING SUBMITTED 5/3/88

1. Handwritten notes indicate changes from FDA text, or additional information supplied to improve consistency among Phenergan® package inserts.
2. Highlighted text without explanatory notes indicates changes or additions to clarify the text or to improve the information flow.

Wyeth®
Phenergan®
(promethazine HCl)
Injection

[illegible]

[illegible]



[illegible]

INSERT HERE:
Promethazine hydrochloride is a racemic compound; the empirical formula is $C_{17}H_{20}N_2S \cdot HCl$ and its molecular weight is 320.88. The pH for the drug product is between 4.0 and 5.5.

[illegible]

Clinical Pharmacology

DELETE THIS PARAGRAPH. SUBSTITUTE THE FOLLOWING:

[illegible]

[illegible]

[illegible]

[illegible]

[illegible]

and Usage

[illegible]

[redacted]

END PARAGRAPH WITH:
promethazine or other phenothiazines.

ADD THE FOLLOWING WARNINGS:

Promethazine may lower seizure threshold. This should be taken into consideration when administering to persons with known seizure disorders or in combination with narcotics or local anesthetics which may also affect seizure threshold.

Tot differ slightly in an effort to be consistent with tot for tablet and Suppository dosage forms

[redacted]

The anticholinergic properties of promethazine have resulted in precipitation of acute narrow angle glaucoma, pyloroduodenal obstruction and urinary tract obstruction. Although such conditions have been rare with promethazine, consideration should be given to the risk of these in prescribing promethazine, especially for patients with a known predisposition to these complications such as those with esophageal peptic ulcer or benign prostatic hypertrophy.

Order of these two statements is reversed as compared to FDA letter of March 14, 1985

"There are no data on safety or efficacy of use of promethazine injection to treat an acute asthmatic attack, therefore, such use is not recommended.

"Administration of promethazine has been associated with reported cholestatic jaundice. This should be taken into consideration when interpreting laboratory results and when selecting medication in patients with impaired liver function.

[redacted]

DELETE THESE TWO PARAGRAPHS AND SUBSTITUTE THE INFORMATION FOUND ON THE NEXT PAGE

[redacted]

[redacted]

[redacted]

INADVERTENT INTRAARTERIAL INJECTION

When preparing to give prometharine intravenously, extreme care should be exercised to avoid perivascular extravasation or inadvertent intra-arterial injection. There are reports of severe tissue injury, including necrosis with resultant gangrene requiring amputation, following the injection of prometharine, usually in conjunction with other drugs meant for intravenous use. Although the intravenous route was intended in all these cases, arterial or partial arterial placement of the needle is now suspect. The mechanism of producing this injury is uncertain, however animal experiments with other arteriolar irritants suggest that the primary cause may be platelet aggregation and thrombosis starting distal to the site of injection.

The first indication of this problem is usually the patient's complaint of severe pain or a sensation of fiery burning, roughly following the distribution path of the injected artery. At the first complaint of any pain during the intended intravenous injection of prometharine, the injection should be stopped immediately and evaluated for possible arterial placement of the needle. Blanching may be present early, may be transient or may not be noted at all. Mottled cyanosis and dark discoloration usually follow. Pain is usually persistent and the skin temperature distal to the injection site may be decreased.

There is no established treatment that has been shown to be successful in the management of this condition after it occurs. Post injury injection of vasodilators and/or arterial infusion of parenteral fluids are generally regarded as being of no value in altering outcome. Animal experiments and published individual case reports concerned with a variety of arteriolar irritants suggest that one or more of the following may be of benefit in reducing the area of necrosis:

1. Heparinization with continuous intra-arterial injection of heparin proximal to the site of injury until pain and swelling have subsided (up to two weeks).

2. Sympathetic block (or brachial plexus block in the arm), if anticoagulant therapy permits.

3. Intra-arterial glucocorticoid injection at the site of injury, followed by systemic steroids.

4. A recent case report (non-promethazine drug injury) suggests that intra-arterial urokinase may promote fibrinolysis, even if administered late in treatment.

Since prevention is the only method shown to be effective in dealing with this problem, the following points are among those that should be considered in its prophylaxis:

1. Beware of the close proximity of arteries and veins at commonly used injection sites and consider the possibility of aberrant arteries.

2. When used intravenously, promethazine hydrochloride should be given in a concentration no greater than 25 mg/ml and at a rate not to exceed 25 mg/minute. Injection into an intravenous infusion set that is known to be running properly should decrease the possibility of inadvertently injecting promethazine intra-arterially. In addition, this results in delivery of a lower concentration of any arteriolar irritant.

3. Subcutaneous swelling near the site of injection calls for discontinuation of promethazine administration and reevaluation of the situation. This sign may be indicative of venous extravasation, which may result in localized necrosis, or it may signify partial arterial placement of the needle or catheter.

4. Be aware that the characteristic bright-red color of arterial blood is discolored by contact with promethazine (italics or different print underlined) so that the aspiration of dark blood does not preclude intra-arterial needle placement.

NDA-00005556

Precautions

GENERAL

Promethazine should be used cautiously in persons with cardiovascular disease or with impairment of bone marrow.

use with caution in patients with lower respiratory disease, including asthma.

INFORMATION FOR PATIENTS

Promethazine may cause marked drowsiness or impair the mental and/or physical abilities required for the performance of potentially hazardous tasks, such as driving a vehicle or operating machinery. Ambulatory patients should be told to avoid engaging in such activities until it is known that they do not become unduly drowsy or dizzy from Promethazine therapy. Children should be supervised to avoid potential harm in bike riding or in other hazardous activities.

The concomitant use of alcohol or other central nervous system depressants, including narcotic analgesics, sedatives, hypnotics, and tranquilizers, may have an additive effect and should be avoided or their dosage reduced.

Patients should be advised to report any involuntary muscle movements or unusual sensitivity to sunlight.

DRUG INTERACTIONS

[illegible]

CNS Depressants - The sedative action of promethazine is additive to the sedative effects of other central-nervous-system depressants, including alcohol, narcotic analgesics, antihistamines, tricyclic antidepressants, phenothiazines, and phenothiazines; therefore, these agents should be avoided or administered in reduced dosage to patients receiving promethazine.

When given concomitantly with promethazine hydrochloride, the dose of barbiturates should be reduced by at least one-half, and the dose of narcotics should be reduced by one-quarter to one-half. Dosage must be individualized. Excessive amounts of promethazine relative to a narcotic may lead to restlessness and motor hyperactivity in the patient with pain; these symptoms usually disappear with adequate control of the pain.

Epinephrine - Although reversal of the vasopressor effect of epinephrine has not been reported with promethazine, in case of promethazine overdose levarterenol or phenylephrine should be administered if a vasopressor is needed. Epinephrine should NOT be used.

MAO Inhibitors - Drug interactions, including an increased incidence of extrapyramidal effects, have been reported when some MAO inhibitors and phenothiazines are used concomitantly. Although such a reaction has not been reported with promethazine, the possibility should be considered.

— This last sentence differs slightly from that suggested in FDA's March 24, 1987 letter in an effort to be consistent with tablet and suppository labeling

— This text is consistent with our tablet and Suppository labeling

DELETE THESE FIVE LINES AND SUBSTITUTE THE INFORMATION FOUND DIRECTLY BELOW THEM

DRUG/LABORATORY TEST INTERACTIONS
The following laboratory tests may be affected in patients who are receiving therapy with promethazine hydrochloride:

Pregnancy Tests
Diagnostic pregnancy tests based on immunological reactions between HCG and anti-HCG may result in false-negative or false-positive interpretations.

Glucose Tolerance Test
An increase in blood glucose has been reported in patients receiving promethazine.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY
Long-term animal studies have not been performed to assess the carcinogenic potential of promethazine, nor are there other animal or human data concerning carcinogenicity, mutagenicity, or impairment of fertility with this drug. Promethazine was nonmutagenic in the Salmonella test system of Ames.

PREGNANCY
Teratogenic Effects—Pregnancy Category C
Teratogenic effects have not been demonstrated in rat-feeding studies at doses of 6.25 and 12.5 mg/kg of promethazine. These doses are from approximately 2.1 to 4.2 times the maximum recommended total daily dose of promethazine for a 50-kg subject, depending upon the indication for which the drug is prescribed. Specific studies to test the action of the drug on parturition, lactation, and development of the animal neonate were not done, but a general preliminary study in rats indicated no effect on these parameters.

The text used below incorporates text from previously submitted injection labeling and text from tablets/suppository labeling as requested by FDA

While antihistamines, including promethazine at a daily dosage level of 25 mg/kg intraperitoneally, have been found to produce fetal mortality in rodents, the pharmacological effects of histamine in the rodent do not parallel those in man.

There are no adequate and well-controlled studies of promethazine in pregnant women. Phenergan should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects

with respect to the possible adverse effect on fetal development. Therefore,

Promethazine administered during labor and delivery may inhibit platelet aggregation in the newborn. The clinical significance of this effect is unknown. Text that is highlighted was added in an effort to be consistent with text which was requested by the FDA for suppository labeling (letter of May 26, 1987 - Bateman to Battista).

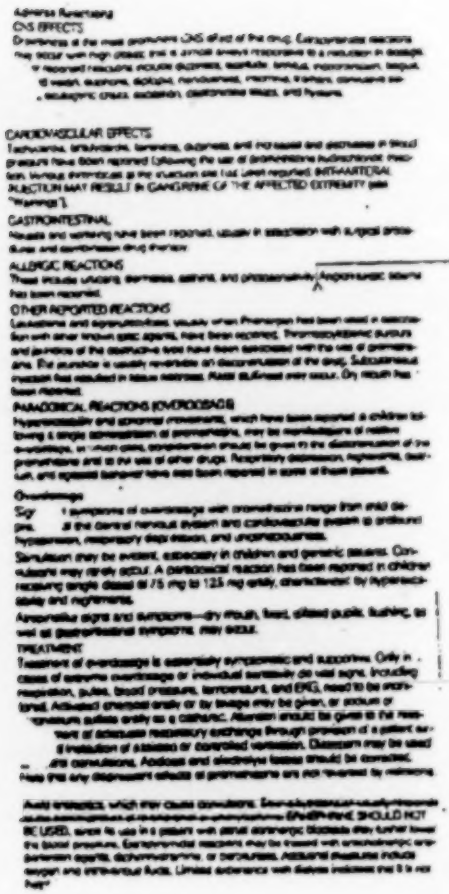
LABOR AND DELIVERY
Phenergan, in appropriate dosage form, may be used alone or as an adjunct to narcotic analgesics during labor and delivery. (See "Indications and Usage" and "Dosage and Administration.")
See also "Nonteratogenic Effects."

Limited data suggest that the use of Phenergan as a sedative during labor and delivery does not have an appreciable effect on the duration of labor or delivery or in increasing the chances that the newborn will require any type of intervention in the process of delivery when given as recommended. The effect on the later growth, development or functional maturation of the newborn when Phenergan has been used during labor and delivery is unknown.

NURSING MOTHERS
It is not known whether promethazine is excreted in human milk. Caution should be exercised when promethazine is administered to a nursing woman.

Pediatric Use

See Warnings - "Use in Children" and Dosage and Administration



INSERT HERE:
Occurrence of photosensitivity may be a contraindication to further treatment with promethazine or related drugs.

REPLACE THE SECOND SENTENCE WITH THE FOLLOWING:
The treatment of choice for resulting hypotension is administration of intravenous fluids, accompanied by repositioning if indicated. In the event that vasopressors are considered for the management of severe hypotension which does not respond to intravenous fluids and repositioning, the administration of levarterenol or phenylephrine should be considered.

DOSAGE AND ADMINISTRATION

[illegible] drug products should be inspected visually [illegible] particulate matter and discoloration prior to administration whenever solution and container permit.

Injection

Do not use Phenergan if solution is discolored or contains a precipitate.

To avoid the possibility of physical and/or chemical incompatibility, consult specialized literature before diluting with any injectable solution or combining with any other medication. Do not use if there is a precipitate or any sign of incompatibility.

Important Notes on Administration

The preferred parenteral route of administration for promethazine hydrochloride is by deep intramuscular injection. The proper intravenous administration of this product is well-[illegible], but use of the route is not without some hazard.

INADVERTENT INTRAARTERIAL INJECTION CAN RESULT IN GANGRENE OF THE AFFECTED EXTREMITY (see "Warnings"). SUBCUTANEOUS INJECTION IS CONTRA[illegible]ATED, AS IT MAY RESULT IN TISSUE NECROSIS (see "Contraindications").

Injection into or near a nerve may result in permanent tissue damage.

When used intravenously, promethazine hydrochloride should be given in concentration no greater than 25 mg/ml, at a rate not to exceed 25 mg per minute; it is preferable to inject through the tubing of an intravenous infusion set that is known to be functioning satisfactorily.

ALLERGIC CONDITIONS

The average adult dose is 25 mg. The dose may be repeated within two hours if necessary, but continued therapy, if indicated, should be via the oral route as soon as [illegible] permit. After initiation of treatment, dosage should be adjusted [illegible] amount adequate to relieve symptoms. The average adult dose for [illegible] of allergic reactions to blood or plasma is 25 mg.

[illegible]ATION

In hospitalized adult patients, nighttime sedation may be achieved by a dose of 25 to 50 mg of promethazine hydrochloride.

PRE- AND POSTOPERATIVE USE

As an adjunct to pre- or postoperative medication, 25 to 50 mg of promethazine hydrochloride in adults may be combined with appropriately reduced doses of analgesics and appropriate drugs as desired. Dosage of concomitant analgesic or hypnotic medication should be reduced accordingly.

NAUSEA AND VOMITING

For control of nausea and vomiting, the usual adult dose is 12.5 to 25 mg, not to be [illegible] more frequently than every four hours. When used for control of postoperative [illegible] and vomiting, the medication may be administered either intramuscularly or [illegible] and dosage of analgesics and tranquilizers reduced accordingly.

OBSTETRICS

Phenergan in doses of 50 mg will provide sedation and relieve apprehension in the early stages of labor. When labor is definitely established, 25 to 75 mg (average dose, 50 mg) promethazine hydrochloride may be given intramuscularly or intravenously with an appropriately reduced dose of any desired narcotic. Adhesive [illegible] may be [illegible] of excitation. Phenergan with a reduced dose of analgesic may be repeated once or twice at four-hour intervals in the course of a normal labor. A maximum total dose of 100 mg of Phenergan may be administered during a 24-hour period to patients in labor.

CHILDREN

In children under the age of 12 years, the dosage should not exceed half that of the suggested adult dose. As an adjunct to premedication, the suggested dose is 0.5 mg per lb. of body weight in combination with an equal dose of narcotic or barbiturate and the appropriate dose of an appropriate drug. Antiemetics should not be used in vomiting of unknown etiology in children.

DELETE THIS SENTENCE

ADD THE FOLLOWING SENTENCE AS THE FIRST PARAGRAPH UNDER THE SUBCATEGORY "CHILDREN":
Phenergan Injection should not be used in children less than 2 years of age.

(See Warnings).

How Supplied

Phenergan® (promethazine HCl) Injection, Wyeth®, is available in packages of 25 ampuls of 1 ml, as follows:
25 mg per ml., NDC 0008-0463
50 mg per ml., NDC 0008-0455

Protect from light.

INSERT HERE:
Store at room temperature, approximately 25°C (77°F).

ALSO AVAILABLE

Phenergan® (promethazine HCl) Injection, Wyeth®, is also available in TUBEX® Sterile Cartridge-Needle Units, [illegible] in packages of 10 TUBEX (1 ml, [illegible]), as follows:

25 mg per mL, NDC 0008-0416
50 mg per mL, NDC 0008-0417

Wyeth Laboratories Inc., Philadelphia, PA 19101
[illegible]
Printed in USA

345

NDA 00005560

LETTER FROM WYETH TO FDA DATED AUGUST 6, 1996 (EXHIBIT A TO DEFENDANT'S RENEWED MOTION FOR JUDGMENT AS A MATTER OF LAW EXHIBIT 12)

WYETH-AYERST [logo] *RESEARCH*

P.O. BOX 8299, PHILADELPHIA, PA 19101-8299 • *(610) 902-3710*
FAX: (610) 964-5973

Division of American Home Products Corporation

U.S. REGULATORY AFFAIRS

[handwritten: SPD-009 BL]

August 6, 1996

Stamp: ORIGINAL/DUPLICATE

Stamp: SUPPL AMENDEMENT

Stamp: "CENTER FOR DRUG
REC'D
AUG 0 8 1996
HFD-570
EVALUATION AND RESEARCH"

NDA No. 8-857/S-009

John Jenkins, M.D., Director
Division of Pulmonary Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
HDF-570, Room 10B-03
5600 Fishers Lane
Rockville, MD 20857-1706

Dear Mr. Jenkins:

Reference is made to our approved New Drug Application No. 8-857 for Phenergan® (promethazine hydrochloride) Injection as well as to our September 21, 1981 supplemental application (S-009) and subsequent amendments, providing draft package inserts revised to conform with content and format labeling requirements for prescription drug products. Reference is also made to the January 7, 1992 submission by Wyeth-Ayerst of an "administrative record" of S-009, which included the package insert then in use with Phenergan Injection ampul packages. Reference is also made to the telephone call of July 2, 1996 from Dr. Susan Johnson of the Division to the undersigned requesting submission of the current package inserts for Phenergan Injection.

Several minor revisions have occurred in the labeling of Phenergan Injection since the submission in 1992 of the then current ampul insert. Note also that identical inserts were utilized for both Phenergan Tubex® and Phenergan ampuls, except for description and usage information specific to the Tubex Sterile Cartridge Unit, and the sulfite warning, which is specific to the ampul formulation. Attachment 1 contains copies of the current package insert for Phenergan Injection packaged in Tubex® Sterile Cartridge Units, identified as CI 3727-5. The differences between this insert and the insert submitted in 1992 (other than the exceptions described above) are as follows.

Title Area:	Deletion of "Wyeth®"; addition of new log
Description section:	Addition of the statement "Sealed under nitrogen."

How Supplied section:	Deletion of "Wyeth®"; addition of the statement **"Do not use if solution is discolored or contains a precipitate."**
Signature Area:	Addition of new logo; revision of the signature to read: Wyeth Laboratories Inc. A Wyeth-Ayerst Company

The manufacture of Phenergan® Injection ampuls has recently been transferred to another site, ESI (Elkins-Sinn Inc.) in Cherry Hill, New Jersey. ESI, another American Home Products Corporation subsidiary, manufactures the product under their Abbreviated New Drug Application (ANDA) for promethazine hydrochloride injection. The current package insert for the ampuls (Attachment 2; CI 4807-1) utilizes the ANDA labeling, and you will therefore notice the following minor differences between this insert and the labeling of the NDA (Tubex®) product (other than the exceptions described above).

Description section:	Begins with an additional statement which reads "Promethazine hydrochloride Injection, USP is a sterile solution for deep intramuscular or intravenous administration." Addition of molecular weight and chemical formula
Clinical Pharmacology:	This heading is used instead of "Actions"
Indications and Usage:	This heading is used instead of "Indications"

Contraindications:	In the first sentence, there is a comma between the words "sedative" and "hypnotics"
Warnings:	Under "Use in Children", the second paragraph (which begins "Caution should be exercised...") is bolded
Dosage and Administration:	The first and second sentences of the second paragraph are bolded
Management of Overdosage:	The sentence which begins "Parenteral drug products should be inspected..." appears (in bold) at the end of this section; whereas it appears at the end of the "Dosage and Administration" section in the Tubex insert."
How Supplied:	The subheading "Storage" does not appear in the Tubex insert
	The ampul insert states **"Keep covered in carton until time of use;"** whereas the Tubex insert states **"Use carton to protect contents from light."**
	The "Do not use if..." and "Store at..." statements are bolded in the Tubex® insert
	The storage temperature range (15°-30°C) in the ampul insert reflects the ANDA labeling
How Supplied (continued):	The "ALSO AVAILABLE" subsection of the ampul insert describes Tubex, while the Tubex insert de-

scribes ampuls.

For your information, we have also included the package insert utilized for the ampuls before the transition to the ANDA product (Attachment 3: CI 3900-3).

Please note that changes to the labeling of the NDA Phenergan Injection product resulting from supplement 009 will be incorporated by ESI into the labeling of the Phenergan ampul product and reported to the Office of Generic Drugs in an appropriate manner.

I hope the enclosed material will facilitate the approval supplement 009 at your earliest convenience. If you have any questions regarding this submission, please contact the undersigned at (610) 902-3761 or Mr. John Seneca at (610) 902-3724.

Sincerely,

WYETH-AYERST LABORATORIES

/s/

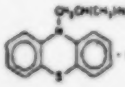
James J. O'Shaughnessy
Associate Director
U. S. Regulatory Affairs

JOS:JS:\a:1081.phe

ATTACHMENT 1

Phenergan®
(promethazine HCl)
Injection

Description
Promethazine HCl (10*H*-phenothiazine-10-ethanamine, *N,N,α*-trimethyl-, monohydrochloride) has the following structural formula:



Each mL of the TUBEX® and TUBEX® BLUNT POINTE™ Sterile Cartridge Units contains either 25 or 50 mg promethazine hydrochloride with 0.1 mg edetate disodium, 0.04 mg calcium chloride, not more than 5 mg monothioglycerol and 5 mg phenol with sodium acetate-acetic acid buffer. Sealed under nitrogen.

Actions
Promethazine hydrochloride, a phenothiazine derivative, possesses antihistaminic, sedative, antimotion-sickness, antiemetic, and anticholinergic effects. The duration of action is generally from four to six hours. The major side reaction of this drug is sedation. As an antihistamine, it acts by competitive antagonism but does not block the release of histamine. It antagonizes in varying degrees most but not all of the pharmacological effects of histamine.

Indications
The injectable form of promethazine hydrochloride is indicated for the following conditions:
1. Amelioration of allergic reactions to blood or plasma.
2. In anaphylaxis as an adjunct to epinephrine and other standard measures after the acute symptoms have been controlled.
3. For other uncomplicated allergic conditions of the immediate type when oral therapy is impossible or contraindicated.
4. Active treatment of motion sickness.
5. Preoperative, postoperative, and obstetric (during labor) sedation.
6. Prevention and control of nausea and vomiting associated with certain types of anesthesia and surgery.
7. As an adjunct to analgesics for the control of postoperative pain.
8. For sedation and relief of apprehension and to produce light sleep from which the patient can be easily aroused.
9. Intravenously in special surgical situations, such as repeated bronchoscopy, ophthalmic surgery, and poor-risk patients, with reduced amounts of meperidine or other narcotic analgesic as an adjunct to anesthesia and analgesia.

Contraindications
Promethazine is contraindicated in comatose states, in patients who have received large amounts of central-nervous-system depressants (alcohol, sedative hypnotics, including barbiturates, general anesthetics, narcotics, narcotic analgesics, tranquilizers, etc.), and in patients who have demonstrated an idiosyncrasy or hypersensitivity to promethazine.

Under no circumstances should promethazine be given by intra-arterial injection due to the likelihood of severe arteriospasm and the possibility of resultant gangrene (see "Warnings").

Phenergan injection should not be given by the subcutaneous route; evidence of chemical irritation has been noted, and necrotic lesions have resulted on rare occasions following subcutaneous injection. The preferred parenteral route of administration is by deep intramuscular injection.

Warnings
Promethazine may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks, such as driving a vehicle or operating machinery. The concomitant use of alcohol, sedative hypnotics (including barbiturates), general anesthetics, narcotics, narcotic analgesics, tranquilizers or other central-nervous-system depressants may have an additive sedative effect. Patients should be warned accordingly.

USAGE IN PREGNANCY
The safe use of promethazine has not been established with respect to the possible adverse effects upon fetal development. Therefore, the need for the use of this drug during pregnancy should be weighed against the possible but unknown hazards to the developing fetus.

USE IN CHILDREN
Excessively large dosages of antihistamines, including promethazine, in children may cause hallucinations, convulsions, and sudden death. In children who are acutely ill associated with dehydration, there is an increased susceptibility to dystonias with the use of promethazine hydrochloride injection.

CAUTION SHOULD BE EXERCISED WHEN ADMINISTERING PHENERGAN TO CHILDREN. ANTIEMETICS ARE NOT RECOMMENDED FOR TREATMENT OF UNCOMPLICATED VOMITING IN CHILDREN, AND THEIR USE SHOULD BE LIMITED TO PROLONGED VOMITING OF KNOWN ETIOLOGY. THE EXTRAPYRAMIDAL SYMPTOMS WHICH CAN OCCUR SECONDARY TO PHENERGAN ADMINISTRATION MAY BE CONFUSED WITH THE CNS SIGNS OF UNDIAGNOSED PRIMARY DISEASE, e.g., ENCEPHALOPATHY OR REYE'S SYNDROME. THE USE OF PHENERGAN SHOULD BE AVOIDED IN CHILDREN WHOSE SIGNS AND SYMPTOMS MAY SUGGEST REYE'S SYNDROME, OR OTHER HEPATIC DISEASES.

USE IN THE ELDERLY (APPROXIMATELY 60 YEARS OR OLDER)
Since therapeutic requirements for sedative drugs tend to be less in elderly patients, the dosage of Phenergan should be reduced for these patients.

OTHER CONSIDERATIONS
Drugs having anticholinergic properties should be used with caution in patients with asthmatic attack, narrow-angle glaucoma, prostatic hypertrophy, stenosing peptic ulcer, pyloroduodenal obstruction, and bladder-neck obstruction.

Phenergan should be used with caution in patients with bone-marrow depression. Leukopenia and agranulocytosis have been reported, usually when Phenergan has been used in association with other known toxic agents.

INADVERTENT INTRA-ARTERIAL INJECTION
Due to the close proximity of arteries and veins in the areas most commonly used for intravenous injection, extreme care should be exercised to avoid perivascular extravasation or inadvertent intra-arterial injection. Reports compatible with inadvertent intra-arterial injection of promethazine, usually in conjunction with other drugs intended for intravenous use, suggest that pain, severe chemical irritation, severe spasm of distal vessels, and resultant gangrene requiring amputation are likely under such circumstances. Intravenous injection was intended in all the cases reported, but perivascular extravasation or arterial placement of the needle is now suspect. There is no proven successful management of this condition after it occurs, although sympathetic block and heparinization are commonly employed during the acute management because of the results of animal experiments with other known arterial irritants. Aspiration of dark blood does not preclude intra-arterial needle placement, because blood is discolored upon contact with promethazine. Use of syringes with rigid plungers or of small bore needles might obscure typical arterial backflow if this is relied upon alone.

When used intravenously, promethazine hydrochloride should be given in a concentration no greater than 25 mg per mL, and at a rate not to exceed 25 mg per minute. When administering any irritant drug intravenously, it is usually preferable to inject it through the tubing of an intravenous infusion set that is known to be functioning satisfactorily. In the event that a patient complains of pain during intended intravenous injection of promethazine, the injection should immediately be stopped to provide for evaluation of possible arterial placement or perivascular extravasation.

Precautions
Promethazine may significantly affect the actions of other drugs. It may increase, prolong, or intensify the sedative action of central-nervous-system depressants, such as alcohol, sedative hypnotics (including barbiturates), general anesthetics, narcotics, narcotic analgesics, tranquilizers, etc. When given concomitantly with promethazine hydrochloride, the dose of barbiturates should be reduced by at least one-half, and the dose of narcotics should be reduced by one-quarter to one-half. Dosage must be individualized. Excessive amounts of promethazine relative to a narcotic may lead to restlessness and motor hyperactivity in the patient with pain; these symptoms usually disappear with adequate control of the pain. Promethazine should be used cautiously in persons with cardiovascular disease or impairment of liver function.

Although reversal of the vasopressor effect of epinephrine has not been reported with promethazine, the possibility should be considered in case of promethazine overdose.

Adverse Reactions
CNS EFFECTS
Drowsiness is the most prominent CNS effect of this drug. Extrapyramidal reactions may occur with high doses; this is almost always responsive to a reduction in dosage. Other reported reactions include dizziness, lassitude, tinnitus, incoordination, fatigue, blurred vision, euphoria, diplopia, nervousness, insomnia, tremors, convulsive seizures, oculogyric crises, excitation, catatonic-like states, and hysteria.

CARDIOVASCULAR EFFECTS
Tachycardia, bradycardia, faintness, dizziness, and increases and decreases in blood pressure have been reported following the use of promethazine hydrochloride injection. Venous thrombosis at the injection site has been reported. INTRA-ARTERIAL INJECTION MAY RESULT IN GANGRENE OF THE AFFECTED EXTREMITY (see "Warnings").

GASTROINTESTINAL
Nausea and vomiting have been reported, usually in association with surgical procedures and combination drug therapy.

ALLERGIC REACTIONS
These include urticaria, dermatitis, asthma, and photosensitivity. Angioneurotic edema has been reported.

OTHER REPORTED REACTIONS
Leukopenia and agranulocytosis, usually when Phenergan has been used in association with other known toxic agents, have been reported. Thrombocytopenic purpura and jaundice of the obstructive type have been associated with the use of promethazine. The jaundice is usually reversible on discontinuation of the drug. Subcutaneous injection has resulted in tissue necrosis. Nasal stuffiness may occur. Dry mouth has been reported.

LABORATORY TESTS
The following laboratory tests may be affected in patients who are receiving therapy with promethazine hydrochloride:

Pregnancy Tests — Diagnostic pregnancy tests based on immunological reactions between HCG and anti-HCG may result in false-negative or false-positive interpretations.

Glucose Tolerance Test — An increase in glucose tolerance has been reported in patients receiving promethazine hydrochloride.

PARADOXICAL REACTIONS (OVERDOSAGE)
Hyperexcitability and abnormal movements, which have been reported in children following a single administration of promethazine, may be manifestations of relative overdosage, in which case, consideration should be given to the discontinuation of the promethazine and to the use of other drugs. Respiratory depression, nightmares, delirium, and agitated behavior have also been reported in some of these patients.

Drug Interactions
NARCOTICS AND BARBITURATES
The CNS-depressant effects of narcotics are additive with promethazine hydrochloride.

Drug interactions, including an increased incidence of extrapyramidal effects, have been reported when some MAOI and phenothiazines are used concomitantly. Although such a reaction has not been reported with promethazine, the possibility should be considered.

Dosage and Administration

The preferred parenteral route of administration for promethazine hydrochloride is by deep intramuscular injection. The proper intravenous administration of this product is well tolerated, but use of this route is not without some hazard.

INADVERTENT INTRA-ARTERIAL INJECTION CAN RESULT IN GANGRENE OF THE AFFECTED EXTREMITY [see "Warnings"]. SUBCUTANEOUS INJECTION IS CONTRAINDICATED, AS IT MAY RESULT IN TISSUE NECROSIS (see "Contraindications"). When used intravenously, promethazine hydrochloride should be given in concentration no greater than 25 mg/mL at a rate not to exceed 25 mg per minute; it is preferable to inject through the tubing of an intravenous infusion set that is known to be functioning satisfactorily.

The TUBEX® BLUNT POINTE™ Sterile Cartridge Unit is suitable for substances to be administered intravenously only. It is intended for use with injection sets specifically manufactured as "needle-less" injection systems. TUBEX® BLUNT POINTE™ is compatible with Abbott's LifeShield® preplerced reseal injection site, Baxter's InterLink® Injection Site, and B. Braun Medical's SafeSite® Reflux Valve. Consult manufacturer's recommendations regarding "Directions for Use" of the "needle-less" system. It is also intended for admixture with, and convenient administration of, various medicaments when using Drug Vial Adapters for "needle-less" injection systems.

The TUBEX® Sterile Cartridge-Needle Unit is suitable for substances to be administered intravenously or intramuscularly.

ALLERGIC CONDITIONS

The average adult dose is 25 mg. This dose may be repeated within two hours if necessary, but continued therapy, if indicated, should be via the oral route as soon as existing circumstances permit. After initiation of treatment, dosage should be adjusted to the smallest amount adequate to relieve symptoms. The average adult dose for amelioration of allergic reactions to blood or plasma is 25 mg.

SEDATION

In hospitalized adult patients, nighttime sedation may be achieved by a dose of 25 to 50 mg of promethazine hydrochloride.

PRE- AND POSTOPERATIVE USE

As an adjunct to pre- or postoperative medication, 25 to 50 mg of promethazine hydrochloride in adults may be combined with appropriately reduced doses of analgesics and atropine-like drugs as desired. Dosage of concomitant analgesic or hypnotic medication should be reduced accordingly.

NAUSEA AND VOMITING

For control of nausea and vomiting, the usual adult dose is 12.5 to 25 mg, not to be repeated more frequently than every four hours. When used for control of postoperative nausea and vomiting, the medication may be administered either intramuscularly or intravenously and dosage of analgesics and barbiturates reduced accordingly.

OBSTETRICS

Phenergan in doses of 50 mg will provide sedation and relieve apprehension in the early stages of labor. When labor is definitely established, 25 to 75 mg (average dose, 50 mg) promethazine hydrochloride may be given intramuscularly or intravenously with an appropriately reduced dose of any desired narcotic. Amnesic agents may be administered as necessary. If necessary, Phenergan with a reduced dose of analgesic may be repeated once or twice at four-hour intervals in the course of a normal labor. A maximum total dose of 100 mg of Phenergan may be administered during a 24-hour period to patients in labor.

CHILDREN

In children under the age of 12 years, the dosage should not exceed half that of the suggested adult dose. As an adjunct to premedication, the suggested dose is 0.5 mg per lb. of body weight in combination with an equal dose of narcotic or barbiturate and the appropriate dose of an atropine-like drug. Antiemetics should not be used in vomiting of unknown etiology in children.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Management of Overdosage

Signs and symptoms of overdosage range from mild depression of the central nervous system and cardiovascular system to profound hypotension, respiratory depression, and unconsciousness. Stimulation may be evident, especially in children and geriatric patients. Atropine-like signs and symptoms — dry mouth, fixed, dilated pupils, flushing, etc., as well as gastrointestinal symptoms, may occur. The treatment of overdosage is essentially symptomatic and supportive. Early gastric lavage may be beneficial if promethazine has been taken orally. Centrally acting emetics are of little use.

Avoid analeptics, which may cause convulsions. Severe hypotension usually responds to the administration of levarterenol or phenylephrine. EPINEPHRINE SHOULD NOT BE USED, since its use in a patient with partial adrenergic blockage may further lower the blood pressure. Extrapyramidal reactions may be treated with antiCholinergic antiparkinson agents, diphenhydramine, or barbiturates. Additional measures include oxygen and intravenous fluids. Limited experience with dialysis indicates that it is not helpful.

How Supplied

Phenergan® (promethazine HCl) Injection is available in the following dosage strengths in TUBEX® BLUNT POINTE™ Sterile Cartridge Units and Sterile Cartridge-Needle Units, packaged in boxes of 10 TUBEX as follows:

25 mg per mL, NDC 3008-0416-50, 1 mL size Blunt Pointe™.

25 mg per mL, NDC 3008-0416-01, 1 mL size (22 gauge x 1-1/4 inch needle).

50 mg per mL, NDC 3008-0417-01, 1 mL size (22 gauge x 1-1/4 inch needle).

Store at room temperature, between 15°-25° C (59°-77° F).

Protect from light.

Use carton to protect contents from light.

Do not use if solution is discolored or contains a precipitate.

ALSO AVAILABLE:

Ampuls of 1 mL, in packages of 25 and 100, as follows:

25 mg per mL, NDC 0008-0063-01

50 mg per mL, NDC 0008-0476-01

* * *

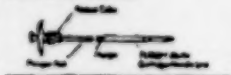
AND TUBEX FAST-TRAK SYRINGE HAVE BEEN DISCONTINUED AND REPLACED BY THE TUBEX INJECTOR. EXCHANGE OF THESE DISCONTINUED SYRINGES IS AVAILABLE, FREE OF CHARGE, FROM YOUR WYETH-AYERST SALES REPRESENTATIVE, OR FROM WYETH-AYERST DIRECTLY. FOR LOADING AND UNLOADING INFORMATION ON THESE DISCONTINUED SYRINGES, CONTACT THE MEDICAL AFFAIRS DEPARTMENT, AT WYETH-AYERST LABORATORIES, P.O. BOX 8299, PHILADELPHIA, PA 19101.

TUBEX® Injector

NOTE: The TUBEX® Injector is reusable; do not discard.

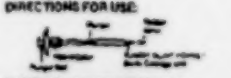
TUBEX® Sterile Cartridge-Needle Unit

DIRECTIONS FOR USE:

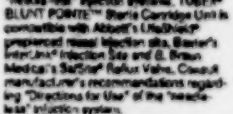


TUBEX® BLUNT POINTE™ Sterile Cartridge Unit

DIRECTIONS FOR USE:



TUBEX® BLUNT POINTE™ Sterile Cartridge Unit is intended for use with injection sets specifically manufactured as "needle-less" injection systems. TUBEX® BLUNT POINTE™ Sterile Cartridge Unit is compatible with Abbott's LifeShield® preplerced reseal injection site, Baxter's InterLink® Injection Site and B. Braun Medical's SafeSite® Reflux Valve. Consult manufacturer's recommendations regarding "Directions for Use" of the "needle-less" injection system.



To load a TUBEX® Sterile Cartridge Unit into the TUBEX® injector:

1. Turn the ribbed collar to the "OPEN" position until it stops.

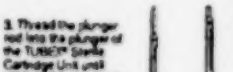
TUBEX® Sterile Cartridge-Needle Unit

TUBEX® BLUNT POINTE™ Sterile Cartridge Unit

2. Hold the injector with the open end up and fully insert the TUBEX® Sterile Cartridge Unit. Firmly tighten the ribbed collar in the direction of the "CLOSE" arrow.

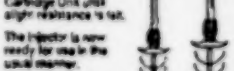
3. Thread the plunger rod into the plunger of the TUBEX® Sterile Cartridge Unit until slight resistance is felt.

The injector is now ready for use in the usual manner.

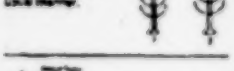


To load an E.S.I. DOSETTE® Sterile Cartridge-Needle Unit into the TUBEX® Injector:

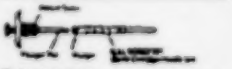
1. Turn the ribbed collar to the "OPEN" position until it stops.



2. Hold the injector with the open end up and fully insert the E.S.I. DOSETTE® Sterile Cartridge-Needle Unit. Firmly tighten the ribbed collar in the direction of the "CLOSE" arrow.



3. Thread the plunger rod into the plunger of the E.S.I. DOSETTE® Sterile Cartridge-Needle Unit until slight resistance is felt.



4. Engage the needle cap assembly by pulling the cap down over the silver cartridge hub. The needle is fully engaged when the silver hub is completely covered.

The injector is now ready for use in the usual manner.

To administer TUBEX®/DOSETTE® Sterile Cartridge-Needle Units:

Method of administration is the same as with conventional syringe. Remove needle cover by grasping it securely; twist and pull. Introduce needle into patient, aspirate by pulling back slightly on the plunger, and inject.

To administer TUBEX® BLUNT POINTE™ Sterile Cartridge Units "Needle-less" IV set administration is similar to administration with conventional syringes. Remove rubber cover by grasping it securely, twist and pull. For B. Braun Medical's SafeSite® Reflux Valves, aseptically swab the luer slip fitting of the BLUNT POINTE™ sterile cartridge tip assembly with a sterile, individually wrapped, saturated 70% Isopropyl Alcohol swab. This action will remove the lubricant coating from the tip to facilitate a tight seal. Introduce TUBEX® BLUNT POINTE™ Sterile Cartridge Unit into the "needle-less" IV set as per manufacturer's "Directions for Use."

To remove the empty TUBEX®/DOSETTE® Cartridge Unit and dispose into a vertical disposal container:

1. Do not recap the needle/point. Disengage the plunger rod.

2. Hold the injector, needle/point down, over a vertical disposal container and loosen the ribbed collar. TUBEX®/DOSETTE® Cartridge Unit will drop into the container.

3. Discard the cover.

To remove the empty TUBEX®/DOSETTE® Cartridge Unit and dispose into a horizontal (mailbox) disposal container:

1. Do not recap the needle/point. Disengage the plunger rod.

2. Open the horizontal (mailbox) disposal container, insert TUBEX®/DOSETTE® Cartridge Unit, needle/point pointing down, halfway into container. Close the container lid on cartridge. Loosen ribbed collar. TUBEX®/DOSETTE® Cartridge Unit will drop into the container.

3. Discard the cover.

The TUBEX® injector is reusable and should not be discarded.

Used TUBEX®/DOSETTE® Cartridge Units should not be employed for parenteral injections or as multiple-dose containers. They are intended to be used only once and discarded.

NOTE: Any graduation markings on TUBEX®/DOSETTE® Sterile Cartridge Units are to be used only as a guide in mixing, withdrawing, or administering measured doses.

Wyeth-Ayerst does not recommend and will not accept responsibility for the use of any cartridge-needle units or needle-less units other than TUBEX® or E.S.I. DOSETTE® Cartridge Units in the TUBEX® Injector.

INTERNAL WYETH MEMORANDUM DATED JANUARY 30, 1997 (DEFENDANT'S TRIAL EXHIBIT U)

[logo]

INTERNAL CORRESPONDENCE

to File	from James O'Shaughnessy (initials)
company	company W-AR located 170/2
subject Phenergan® Injection Pending Supplements	date January 30, 1997

Stamp: CONFIDENTIAL

On January 29, 1997, I spoke with Ms. Beverly Gallauresi of the Division of Pulmonary Drug Products (DPDP) regarding the following pending supplemental applications for Phenergan Injection.

* * *

NDA No. 8-857/S-009
Labeling Supplement

This supplement was initially filed in 1981. There have been numerous amendments and submissions of draft labeling and supportive documentation over the years. In June 1996, Wyeth-Ayerst was asked to prepare a narrative outlining the differences in the text of the currently approved package insert and any text changes since 1992. During the remainder of 1996, the DPDP consistently advised that the labeling review was nearing an end.

During today's conversation, Ms. Gallauresi indicated that the labeling review is complete. However, because it has taken the DPDP so long to complete the review, they are taking extra care to make sure they have dotted every "i" and crossed every "t." She advised me that a letter is circulating within the DPDP for final review and comments. Ms. Gallauresi said she hoped this letter could be FAXed to us in the very near future, however, she could not guarantee that this would happen before Friday, February 7, 1997.

JOS:am

cc: Mr. Bathish
Dr. Bernady
Dr. DeVries
Mr. Seneca
Mr. Victoria

LETTER FROM FDA TO WYETH DATED FEBRUARY 21, 1997 (DEFENDANT'S TRIAL EXHIBIT O)

[logo]

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service

Food and Drug Administration
Rockville MD 20857

Stamp: CONFIDENTIAL

Stamp: FEB 21 1997

Stamp: RECEIVED
FEB 26 1997
Mr. J. O'Shaughnessy

cc: JNB, KFB, CSC, VDV,
JOS, JS, JRV, GRO, Log

NDA 8-857/S-009

Wyeth-Ayerst
P.O. Box 8299
Philadelphia, PA 19101-8299

Attention: James J. O'Shaughnessy
Associate Director
U.S. Regulatory Affairs

Dear Mr. O'Shaughnessy:

Reference is made to your supplemental new drug application dated September 21, 1981, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Phenergan (promethazine hydrochloride) Injection.

We acknowledge receipt of your amendments dated May 3, 1988, February 1, March 1, and May 15, 1989, January 7, 1992, and August 6, 1996.

We have completed the review of this supplemental application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to submit final printed labeling (FPL) revised as follows.

The following comments are provided regarding the versions of the Phenergan Tubex and Ampul labeling submitted in the August 6, 1996 amendment. Please note that the term "current labeling" refers to these versions.

1. Identical inserts should be utilized for both Phenergan Tubex and Phenergan Ampuls, except for description and usage information specific to the Tubex Sterile Cartridge Unit and the sulfite warning, which is specific to the ampul formulation.

2. The format for the trade name should be "Phenergan (promethazine HCL) Injection" and should be used consistently for both the tubex and ampul products. Within the package inserts, the term "promethazine hydrochloride" or "promethazine HCL" is appropriate for the DESCRIPTION and the CLINICAL PHARMACOLOGY sections, however, the trade name should be used consistently throughout the remainder of the labeling to refer to the drug product.

3. The DESCRIPTION section of both the tubex and ampul inserts should include the molecular weight, empirical formula and pH. Both inserts

should state that promethazine hydrochloride is a racemic compound and the Chemical name should be modified to read "... monohydrochloride±)."

4. The DESCRIPTION section should include a statement which indicates that the drug is "sterile and pyrogen free" and that it is "sealed under nitrogen."

5. The following statement should be added to the DESCRIPTION section. "Phenergan (promethazine HCL) Injection is a clear, colorless solution. The product is light sensitive. It should be inspected before use and discarded if either color or particulate is observed."

6. The CLINICAL PHARMACOLOGY section should be titled as such and should read as follows.

   Promethazine hydrochloride is a phenothiazine derivative which possesses antihistaminic, sedative, antimotion-sickness, antiemetic and anticholinergic effects. Promethazine is a competitive H_1 receptor antagonist, but does not block the release of histamine. Structural differences from the neuroleptic phenothiazines results in its relative lack (1/10) of dopamine antagonist properties. In therapeutic doses, promethazine hydrochloride produces no significant effects on the cardiovascular system. Clinical effects are generally apparent within 5 minutes of an intravenous injection and within 20 minutes of an intramuscular injection. Duration of action is four to six hours, although effects may persist up to 12 hours. Promethazine hydrochloride is metabolized in the liver, with

the sulfoxides of promethazine and N-desmethylpromethazine being the predominant metabolites appearing in the urine.

7. The INDICATIONS AND USAGE section should be titled as such in both the tubex and ampul labeling.

8. It is recommended that the sequence of indications in the INDICATIONS AND USAGE section be ordered in the same manner as the DOSAGE AND ADMINISTRATION section, or vice versa.

9. The concurrent use of promethazine with other phenothiazine drugs should be limited, however, it is not clear that this interaction is strictly contraindicated as the current CONTRAINDICATIONS section states. These additive interactions may be identified in the Drug Interactions subsection of the PRECAUTIONS section:

10. The WARNINGS section should be modified to read as follows.

SULFITE SENSITIVITY—

a. Phenergan HCL Injection (ampuls only) contains sodium metabisulfite, a sulfite that may cause allergic-type reactions, including anaphylactic symptoms and life-threatening or less severe asthma episodes, in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in nonasthmatic people.

b. **CNS Depression**—Phenergan Injection may impair the mental and physical abilities required for the performance of potentially hazardous tasks, such as driving a vehicle or operating machinery. The impairment may be amplified by concomitant use of other central nervous system depressants such as alcohol, sedative hypnotics (including barbiturates), general anesthetics, narcotics, narcotic analgesics, tranquilizers, etc. (See Information for Patients).

c. **Lower Seizure Threshold**—Phenergan Injection may lower seizure threshold and should be used with caution in persons with seizure disorders or in persons who are using concomitant medications, such as narcotics or local anesthetics, which may also affect seizure threshold.

d. **Bone Marrow Depression**—Phenergan Injection should be used with caution in patients with bone marrow depression. Leukopenia and agranulocytosis have been reported, usually when Phenergan has been used in association with other known marrow toxic agents.

e. **Use in Children**—Retain verbiage in current label. Add "Phenergan Injection is not recommended for use in children less than two years of age."

f. **Inadvertent Intra-arterial Injection**—Retain verbiage in current label.

g. **Visual Inspection**—This product is light sensitive and should be inspected before

use and discarded if either color particulate is observed.

11. Information regarding use in the elderly and use in pregnancy may be moved to the PRECAUTIONS section. The "Other Considerations" subsection can be removed.

12. The PRECAUTIONS section should be divided into subsections as follows:

General

Drugs having anticholinergic properties should be used with caution in patients with narrow angle glaucoma, prostatic hypertrophy, stenosing peptic ulcer, pyloroduodenal obstruction and bladder-neck obstruction.

Phenergan Injection should be used with caution in persons with cardiovascular disease or impairment of liver function.

Information for Patients

Phenergan Injection may impair the mental or physical abilities required for the performance of potentially hazardous tasks, such as driving a vehicle or operating machinery. The use of alcohol, sedative hypnotics (including barbiturates), general anesthetics, narcotics, narcotic analgesics, tranquilizers, etc. with Phenergan Injection may enhance the impairment. Persistent or worsening pain or burning at the injection site should be reported immediately. Avoid prolonged exposure to the sun.

Drug Interactions

This section should be relocated from its current position in the labeling and modified as specified below.

CNS Depressants—Phenergan Injection may increase, prolong or intensify the sedative action of central nervous system depressants such as alcohol, sedative hypnotics (including barbiturates), general anesthetics, narcotics, narcotic analgesics, tranquilizers, etc. When given concomitantly with Phenergan Injection, the dose of barbiturates should be reduced by at least one-half, and the dose of narcotics should be reduced by one-quarter to one-half. Dosage must be individualized. Excessive amounts of Phenergan Injection relative to a narcotic may lead to restlessness and motor hyperactivity in the patient with pain; these symptoms usually disappear with adequate control of the pain.

Epinephrine—Although reversal of the vasopressor effect of epinephrine has not been reported with Phenergan Injection, it is recommended that epinephrine NOT be used in the case of Phenergan Injection overdose.

Anticholinergics—Concomitant use of other agents with anticholinergic properties should be undertaken with caution.

Monoamine Oxidase (MAO) Inhibitors—retain information currently in tubex labeling.

Laboratory Test Interactions

Information from the ADVERSE REACTIONS section of the current labeling should be relocated in this subsection.

Carcinogenesis, Mutagenesis and Impairment of Fertility

Long term animal studies have not been performed to assess the carcinogenic potential of Phenergan Injection, nor are there other animal or human data concerning carcinogenicity, mutagenicity or impairment of fertility. Phenergan Injection was nonmutagenic in the Ames Salmonella test system.

Teratogenic Effects—Pregnancy Category C

Teratogenic effects have not been demonstrated in rat feeding studies at doses of 6.25 and 12.5 mg/kg (approximately 2.1 and 4.2 times the maximum recommended human daily dose) of Phenergan Injection. Daily doses of 25 mg/kg intraperitoneally have been found to produce fetal mortality in rats.

There are no adequate and well-controlled studies of Phenergan Injection in pregnant women. Because animal reproduction studies are not always predictive of human response, Phenergan Injection should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Adequate studies to determine the action of the drug on parturition, lactation and development of the animal neonate have not been conducted.

Use in Labor and Delivery

Phenergan Injection may be used alone or as an adjunct to narcotic analgesics during labor (See DOSAGE AND ADMINISTRATION). Limited data suggest that use of Phenergan Injection during labor and delivery does not have an

appreciable effect on the duration of labor or delivery and does not increase the risk of need for intervention in the newborn. The effect on later growth and development of the newborn is unknown.

Nursing Mothers

It is not known whether Phenergan Injection is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Phenergan Injection is administered to a nursing woman.

Pediatrics

Phenergan Injection should be used with caution in pediatric patients. See WARNINGS Section.

Use in the Elderly (Approximately 60 years or older)

Since therapeutic requirements for sedative drugs tend to be less in geriatric patients, the dosage should be reduced for these patients.

13. The following comments pertain to the ADVERSE REACTIONS section.

    a. The Laboratory Tests subsection should be removed from the ADVERSE REACTIONS section.

    b. In a recent review of the Spontaneous Reporting System database, it was determined that the term "hallucinations" was reported with significant frequency and we believe that the pharmacologic activity of promethazine is such that a causal relationship may be inferred from these data. This

term is currently included in the package insert under WARNINGS, subsection, "Use in Children." We request that it also be added to the ADVERSE REACTIONS, subsection, "CNS Effects."

14. The OVERDOSAGE section should follow the ADVERSE REACTIONS section and should be titled consistently. The remainder of the section is acceptable.

15. The DOSAGE AND ADMINISTRATION section should be modified as follows,

    a. The sentence which ends "...without some hazard." should be followed by "Not for subcutaneous administration."

    b. The sentence which begins "Inadvertent intra-arterial injection ..." should appear in bold. The statement which follows, regarding rate of administration, should be offset in a separate paragraph.

    c. The subsection titled "Children" should contain the statement "Phenergan Injection is not recommended for use in children less than two years of age."

    d. The sentence "Parenteral drug products should be inspected visually ..." should also appear in bold and should be moved to the beginning of the DOSAGE AND ADMINISTRATION section.

16. Regarding the tubex product, the instructions for use refer to a "Tubex injector." This device should be described in the HOW SUPPLIED section.

17. Both Ampuls and Tubex boxes, 25 and 50 mg strength, should describe route of injection as 25 mg—IV or IM, 50 mg—IM only.

Please submit 16 copies of the printed labeling, ten of which are individually mounted on heavy-weight paper or similar material.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Within 10 days after the date of this letter, you are required to amend the supplemental application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of such action FDA may take action to withdraw the application.

If you have any questions, please contact Ms. Beverly Gallauresi, Project Manager, at (301) 827-1054.

Sincerely yours,

/s/

John K. Jenkins, M.D.
Director
Division of Pulmonary Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

LETTER FROM WYETH TO FDA DATED MAY 8, 1998 (DEFENDANT'S TRIAL EXHIBIT N)

WYETH-AYERST [logo] *RESEARCH*

U.S. REGULATORY AFFAIRS

P.O. BOX 8299, PHILADELPHIA, PA 19101-8299 • (610) 902-3710
FAX: (610) 964-5973

May 8, 1998

NDA 8-857/S-009
Phenergan® Injection

John Jenkins, M.D., Director
Division of Pulmonary Drug Products (HDF-570)
Center for Drug Evaluation and Research
Document Control Room 10B-03
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857-1706

Dear Mr. Jenkins:

Reference is made to our approved New Drug Application No. 8-857 for Phenergan® (promethazine hydrochloride) Injection as well as to our September 21, 1981 supplemental application (S-009), and subsequent amendments, providing draft package inserts revised to conform with content and format labeling requirements for prescription drug products. Reference is also made to the February 21, 1997 letter from the Division of Pulmonary Drug Products (DPDP) advising us that S-009 is "approvable," and requesting the submission revised final printed labeling.

The purpose of this communication is to submit the enclosed copies (four) of draft package insert labeling for Phenergan® Injection in Tubex® (Attachment 1) and Phenergan® Injection ampuls (Attachment 2) that has been revised in accordance with the comments contained in the DPDP's February 21, 1997 letter. Please note however the following modifications:

1) Under "CLINICAL PHARMACOLOGY," information has been added on the mean plasma half-life of promethazine following intravenous and intramuscular administration. The supporting references for this information are included as Attachment 3.

2) Under "WARNINGS—Use in Pediatric Patients," the requested statement, "Phenergan Injection is not recommended for use in pediatric patient less than two years of age," has been added in bold, upper case type at the beginning of the section, followed by the bolded paragraph which begins "CAUTION SHOULD BE EXERCISED..."

3) Under "WARNINGS," we propose to retain a section entitled "Other Considerations" containing the following text: "Sedative drugs or CNS depressants should be avoided in patients with a history of sleep apnea" and "Administration of promethazine has been associated with reported cholestatic jaundice." These statements were proposed in the draft labeling previously submitted; they appear in the current Phenergan Tablets and Suppositories package insert and we believe they are appropriate for the labeling of the injection dosage form.

4) Under "Information for Patients," we propose to retain the phrase "cause marked drowsiness" in the

first sentence (ie., "Phenergan Injection may cause marked drowsiness or impair..."). We also propose to include the statements "Pediatric patients should be supervised to avoid potential harm in bike riding or in other hazardous activities" and "Patients should be advised to report any involuntary muscle movements." These statements were proposed in the draft labeling previously submitted; they appear in the current Phenergan Tablets and Suppositories package insert and we believe they are appropriate for the labeling of the injection dosage form.

5) Under "PRECAUTIONS—Pregnancy," we propose to include a subsection titled "Nonteratogenic Effects" with the following text: "Phenergan Injection received within two weeks of delivery may inhibit platelet aggregation in the newborn." This statement was proposed in the draft labeling previously submitted; it appears in the current Phenergan Tablets and Suppositories package insert and we believe it is appropriate for the labeling of the injection dosage form.

6) Under "PRECAUTIONS—Labor and Delivery," the statement "(See also Nonteratogenic Effects)" has been added.

7) Editorial or similarly minor changes have been made throughout the insert, e.g., the word "children" has been replaced with "pediatric patients" where appropriate.

The "OVERDOSAGE" and "DOSAGE AND ADMINISTRATION" sections have been revised to incorporate the recommendations in the February 21, 1997 "approvable" letter, as well as the revisions proposed in S-009 and subsequent amendments. We be-

lieve this reflects the intent of the comments contained in the "approvable" letter with respect to these sections.

In order to facilitate the Agency's review of the modifications described above, we are submitting draft, rather than final printed labeling. The draft labeling consists of work processing copies of the current package inserts for Phenergan Injection in Tubex and Phenergan Injection ampuls which show the changes by means of shading (new text) and strikeout (deleted text). Please note that the current insert for Phenergan Injection in Tubex has undergone a minor revision since the submission of the then current insert on August 6, 1996, ie., the "±" symbol has been added to the chemical name under "DESCRIPTION."

We hope you will find the enclosed labeling satisfactory and will so advise us at your earliest convenience. If you have any questions regarding this submission, please contact the undersigned at 610-902-3775 (fax 610-964-5972) or Mr. John Seneca at 610-902-3724.

Sincerely,

WYETH-AYERST LABORATORIES

/s/

Nanette E. Holston
Manager
U. S. Regulatory Affairs

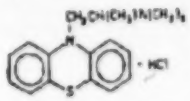
* * *

BEST AVAILABLE COPY

Phenergan®
(promethazine HCl)
Injection

DESCRIPTION

Phenergan (promethazine HCl) Injection is a sterile, pyrogen-free solution for deep intramuscular or intravenous administration. Promethazine HCl (10*H*-phenothiazine-10-ethanamine, *N,N,α*-trimethyl-, monohydrochloride, (±)-) is a racemic compound and has the following structural formula:



$C_{17}H_{20}CN_2S$ MW=320.89

Each mL of the **TUBEX®** and **TUBEX® BLUNT POINTE™** Sterile Cartridge Units contains either 25 or 50 mg promethazine ~~hydrochloride~~ HCl with 0.1 mg edetate disodium, 0.04 mg calcium chloride, not more than 5 mg monothioglycerol, and 5 mg phenol in Water for Injection. The pH range is 4.0 to 5.5, buffered with sodium acetate-acetic acid ~~buffer~~, and it is sealed under nitrogen.

Phenergan (promethazine HCl) Injection is a clear, colorless solution. The product is light sensitive. It should be inspected before use and discarded if either color or particulate is observed.

~~Actions~~ CLINICAL PHARMACOLOGY

Promethazine ~~hydrochloride~~ HCl is a phenothiazine derivative which possesses antihistaminic, sedative, antimotion-sickness, antiemetic, and anticholinergic effects. ~~The major side reaction of this drug is sedation. As an antihistamine, it acts by competitive antagonism but does not block the release of histamine. It antagonizes in varying degrees most but not all of the pharmacological effects of histamine.~~ Promethazine is a competitive H_1 receptor antagonist, but does not block the release of histamine. Structural differences from the neuroleptic phenothiazines results in relatively low (1/10) of dopamine antagonist properties. In therapeutic doses, promethazine HCl produces no significant effects on the cardiovascular system. Clinical effects are generally apparent within 5 minutes of an intravenous injection and within 20 minutes of intramuscular injection. The duration of action is ~~generally~~ from four to six hours, although effects may persist up to 12 hours. Promethazine HCl is metabolized in the liver, with the sulfoxides of promethazine and N-desmethylpromethazine being the predominant metabolites appearing in the urine. Following intravenous administration in healthy volunteers, the plasma half-life for promethazine has been reported to range from 9 to 16 hours. [1] The mean plasma half-life for promethazine after intramuscular administration in healthy volunteers has been reported to be 9.8±3.4 hours. [2]

NDA-00001020

INDICATIONS AND USAGE

~~The injectable form of promethazine hydrochloride~~ Phenergan Injection is indicated for the following conditions:

1. Amelioration of allergic reactions to blood or plasma.
2. In anaphylaxis as an adjunct to epinephrine and other standard measures after the acute symptoms have been controlled.
3. For other uncomplicated allergic conditions of the immediate type when oral therapy is impossible or contraindicated.
~~8~~ 4. For sedation and relief of apprehension and to produce light sleep from which the patient can be easily aroused.
~~4~~ 5. Active treatment of motion sickness.
6. Prevention and control of nausea and vomiting associated with certain types of anesthesia and surgery.
7. As an adjunct to analgesics for the control of postoperative pain.
~~5~~ 8. Preoperative, postoperative, and obstetric (during labor) sedation.
9. Intravenously in special surgical situations, such as repeated bronchoscopy, ophthalmic surgery, and poor-risk patients, with reduced amounts of meperidine or other narcotic analgesic as an adjunct to anesthesia and analgesia.

CONTRAINDICATIONS

~~Promethazine~~ Phenergan Injection is contraindicated in comatose states~~, in patients who have received large amounts of central nervous system depressants (alcohol, sedative hypnotics, including barbiturates, general anesthetics, narcotics, narcotic analgesics, tranquilizers, etc.)~~; and in patients who have demonstrated an idiosyncrasy or hypersensitivity to promethazine or other phenothiazines.

Under no circumstances should ~~promethazine~~ Phenergan Injection be given by intra-arterial injection due to the likelihood of severe arteriospasm and the possibility of resultant gangrene (see "WARNINGS—Inadvertent Intra-arterial Injection").

Phenergan Injection should not be given by the subcutaneous route; evidence of chemical irritation has been noted, and necrotic lesions have resulted on rare occasions following subcutaneous injection. The preferred parenteral route of administration is by deep intramuscular injection.

WARNINGS

CNS Depression

~~Promethazine~~ Phenergan Injection may impair the mental and/~~or~~ physical abilities required for the performance of potentially hazardous tasks, such as driving a vehicle or operating machinery. The impairment may be amplified by concomitant use of other central-nervous-system depressants such as alcohol, sedative-hypnotics (including barbiturates), general anesthetics, narcotics, narcotic analgesics, tranquilizers, etc. (see "PRECAUTIONS—Information for Patients"). ~~or other central nervous system depressants may have an additive sedative effect.~~

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~~Patients should be warned accordingly.~~

Lower Seizure Threshold

Phenergan Injection may lower seizure threshold and should be used with caution in persons with seizure disorders or in persons who are using concomitant medications, such as narcotics or local anesthetics, which may also affect seizure threshold.

Bone-Marrow Depression

Phenergan Injection should be used with caution in patients with bone-marrow depression. Leukopenia and agranulocytosis have been reported, usually when Phenergan has been used in association with other known marrow-toxic agents.

~~USAGE IN PREGNANCY~~

~~The safe use of promethazine has not been established with respect to the possible adverse effects upon fetal development. Therefore, the need for the use of this drug during pregnancy should be weighed against the possible but unknown hazards to the developing fetus.~~

Use in ~~CHILDREN~~ Pediatric Patients

PHENERGAN INJECTION IS NOT RECOMMENDED FOR USE IN PEDIATRIC PATIENTS LESS THAN TWO YEARS OF AGE.

CAUTION SHOULD BE EXERCISED WHEN ADMINISTERING PHENERGAN INJECTION TO ~~CHILDREN~~ PEDIATRIC PATIENTS 2 YEARS OF AGE AND OLDER. ANTIEMETICS ARE NOT RECOMMENDED FOR TREATMENT OF UNCOMPLICATED VOMITING IN ~~CHILDREN~~ PEDIATRIC PATIENTS, AND THEIR USE SHOULD BE LIMITED TO PROLONGED VOMITING OF KNOWN ETIOLOGY. THE EXTRAPYRAMIDAL SYMPTOMS WHICH CAN OCCUR SECONDARY TO PHENERGAN INJECTION ADMINISTRATION MAY BE CONFUSED WITH THE CNS SIGNS OF UNDIAGNOSED PRIMARY DISEASE, e.g., ENCEPHALOPATHY OR REYE'S SYNDROME. THE USE OF PHENERGAN INJECTION SHOULD BE AVOIDED IN ~~CHILDREN~~ PEDIATRIC PATIENTS WHOSE SIGNS AND SYMPTOMS MAY SUGGEST REYE'S SYNDROME OR OTHER HEPATIC DISEASES.

Excessively large dosages of antihistamines, including ~~promethazine~~ Phenergan Injection, in ~~children~~ pediatric patients may cause hallucinations, convulsions, and sudden death. In ~~children~~ pediatric patients who are acutely ill associated with dehydration, there is an increased susceptibility to dystonias with the use of ~~promethazine hydrochloride~~ Phenergan Injection.

~~USE IN THE ELDERLY (APPROXIMATELY 60 YEARS OR OLDER)~~ [TEXT RELOCATED TO PRECAUTIONS]

~~Since therapeutic requirements for sedative drugs tend to be less in elderly patients, the dosage of Phenergan should be reduced for these patients.~~

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Inadvertent Intra-arterial Injection

Due to the close proximity of arteries and veins in the areas most commonly used for intravenous injection, extreme care should be exercised to avoid perivascular extravasation or inadvertent intra-arterial injection. Reports compatible with inadvertent intra-arterial injection of ~~promethazine~~ Phenergan Injection, usually in conjunction with other drugs intended for intravenous use, suggest that pain, severe chemical irritation, severe spasm of distal vessels, and resultant gangrene requiring amputation are likely under such circumstances. Intravenous injection was intended in all the cases reported but perivascular extravasation or arterial placement of the needle is now suspect. There is no proven successful management of this condition after it occurs, although sympathetic block and heparinization are commonly employed during the acute management because of the results of animal experiments with other known arteriolar irritants. Aspiration of dark blood does not preclude intra-arterial needle placement, because blood is discolored upon contact with ~~promethazine~~ Phenergan Injection. Use of syringes with rigid plungers or of small bore needles might obscure typical arterial backflow if this is relied upon alone.

When used intravenously, ~~promethazine hydrochloride~~ Phenergan Injection should be given in a concentration no greater than 25 mg per mL and at a rate not to exceed 25 mg per minute. When administering any irritant drug intravenously, it is usually preferable to inject it through the tubing of an intravenous infusion set that is known to be functioning satisfactorily. In the event that a patient complains of pain during intended intravenous injection of ~~promethazine~~ Phenergan Injection, the injection should be stopped immediately to provide for evaluation of possible arterial placement or perivascular extravasation.

Visual Inspection

This product is light sensitive and should be inspected before use and discarded if either color or particulate is observed.

Other Considerations

Sedative drugs or CNS depressants should be avoided in patients with a history of sleep apnea.

~~Administration of promethazine has been associated with reported cholestatic jaundice.~~

~~Drugs having anticholinergic properties should be used with caution in patients with asthmatic attack, narrow-angle glaucoma, prostatic hypertrophy, stenosing peptic ulcer, pyloroduodenal obstruction, and bladder-neck obstruction.~~ [TEXT RELOCATED TO PRECAUTIONS—GENERAL]

PRECAUTIONS

~~Promethazine may significantly affect the actions of other drugs.~~

General

Drugs having anticholinergic properties should be used with caution in patients with narrow-angle glaucoma, prostatic hypertrophy, stenosing peptic ulcer, pyloroduodenal obstruction, and bladder-neck obstruction. [TEXT RELOCATED FROM WARNINGS—OTHER CONSIDERATIONS]

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~~Promethazine~~ Phenergan Injection should be used cautiously in persons with cardiovascular disease or impairment of liver function.

Information for Patients

Phenergan Injection may cause marked drowsiness or impair the mental or physical abilities required for the performance of potentially hazardous tasks, such as driving a vehicle or operating machinery. The use of alcohol, sedative-hypnotics (including barbiturates), general anesthetics, narcotics, narcotic analgesics, tranquilizers, etc. with Phenergan Injection may enhance impairment. Pediatric patients should be supervised to avoid potential harm in bike riding or in other hazardous activities.

Patients should be advised to report any involuntary muscle movements.

Persistent or worsening pain or burning at the injection site should be reported immediately.

Avoid prolonged exposure to the sun.

Drug Interactions

~~NARCOTICS AND BARBITURATES~~

~~The CNS depressant effects of narcotics and barbiturates are additive with promethazine hydrochloride.~~

CNS Depressants - ~~It~~ Phenergan Injection may increase, prolong, or intensify the sedative action of central-nervous-system depressants, such as alcohol, sedative-hypnotics (including barbiturates), general anesthetics, narcotics, narcotic analgesics, tranquilizers, etc. When given concomitantly with ~~promethazine hydrochloride~~ Phenergan Injection, the dose of barbiturates should be reduced by at least one-half, and the dose of narcotics should be reduced by one-quarter to one-half. Dosage must be individualized. Excessive amounts of ~~promethazine~~ Phenergan Injection relative to a narcotic may lead to restlessness and motor hyperactivity in the patient with pain; these symptoms usually disappear with adequate control of the pain.

Epinephrine - Although reversal of the vasopressor effect of epinephrine has not been reported with ~~promethazine~~ Phenergan Injection, ~~the possibility should be considered~~ it is recommended that epinephrine NOT be used in the case of ~~promethazine~~ Phenergan Injection overdose.

Anticholinergics - Concomitant use of other agents with anticholinergic properties should be undertaken with caution.

Monoamine Oxidase Inhibitors (MAOI) - Drug interactions, including an increased incidence of extrapyramidal effects, have been reported when some MAOI and phenothiazines are used concomitantly. Although such a reaction has not been reported with ~~promethazine~~ Phenergan Injection, the possibility should be considered.

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Laboratory Test Interactions (TEXT RELOCATED FROM ADVERSE REACTIONS)

The following laboratory tests may be affected in patients who are receiving therapy with Phenergan Injection:

Pregnancy Tests - Diagnostic pregnancy tests based on immunological reactions between HCG and anti-HCG may result in false-negative or false-positive interpretations.

Glucose Tolerance Test - An increase in glucose tolerance has been reported in patients receiving promethazine HCl.

Carcinogenesis, Mutagenesis and Impairment of Fertility

Long-term animal studies have not been performed to assess the carcinogenic potential of Phenergan Injection, nor are there other animal or human data concerning carcinogenicity, mutagenicity, or impairment of fertility. Phenergan Injection was nonmutagenic in the Ames *Salmonella* test system.

Pregnancy

Teratogenic Effects - Pregnancy Category C

Teratogenic effects have not been demonstrated in rat feeding studies at doses of 6.25 and 12.5 mg/kg (approximately 2.1 and 4.2 times the maximum recommended human daily dose) of Phenergan Injection. Daily doses of 25 mg/kg intraperitoneally have been found to produce fetal mortality in rats.

There are no adequate and well-controlled studies of Phenergan Injection in pregnant women. Because animal reproduction studies are not always predictive of human response, Phenergan Injection should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Adequate studies to determine the action of the drug on parturition, lactation and development of the animal neonate have not been conducted.

Nonteratogenic Effects

Phenergan Injection received within two weeks of delivery may inhibit platelet aggregation in the newborn.

Labor and Delivery

Phenergan Injection may be used alone or as an adjunct to narcotic analgesics during labor (see "DOSAGE AND ADMINISTRATION"). Limited data suggest that use of Phenergan Injection during labor and delivery does not have an appreciable effect on the duration of labor or delivery and does not increase the risk of need for intervention in the newborn. The effect on later growth and development of the newborn is unknown. (See also "*Nonteratogenic Effects*.")

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Nursing Mothers

It is not known whether Phenergan Injection is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Phenergan Injection is administered to a nursing woman.

Pediatric Use

Safety and effectiveness in pediatric patients under 2 years of age have not been established.

Phenergan Injection should be used with caution in pediatric patients 2 years of age and older (see "WARNINGS—Use in Pediatric Patients").

Use in Geriatric Patients (approximately 60 years or older) [TEXT RELOCATED FROM WARNINGS]

Since therapeutic requirements for sedative drugs tend to be less in geriatric patients, the dosage should be reduced for these patients.

ADVERSE REACTIONS

CNS Effects

Drowsiness is the most prominent CNS effect of this drug. Extrapyramidal reactions may occur with high doses; this is almost always responsive to a reduction in dosage. Other reported reactions include dizziness, lassitude, tinnitus, incoordination, fatigue, blurred vision, euphoria, diplopia, nervousness, insomnia, tremors, convulsive seizures, oculogyric crises, excitation, catatonic-like states, and hysteria, and hallucinations.

Cardiovascular Effects

Tachycardia, bradycardia, faintness, dizziness, and increases and decreases in blood pressure have been reported following the use of ~~promethazine hydrochloride~~ Phenergan Injection. Venous thrombosis at the injection site has been reported. INTRA-ARTERIAL INJECTION MAY RESULT IN GANGRENE OF THE AFFECTED EXTREMITY (see "WARNINGS—Inadvertent Intra-arterial Injection").

Gastrointestinal Effects

Nausea and vomiting have been reported, usually in association with surgical procedures and combination drug therapy.

Allergic Reactions

These include urticaria, dermatitis, asthma, and photosensitivity. Angioneurotic edema has been reported.

Other Reported Reactions

Leukopenia and agranulocytosis, usually when Phenergan has been used in association with other known marrow-toxic agents, have been reported. Thrombocytopenic purpura and jaundice of the obstructive type have been associated with the use of ~~promethazine~~ Phenergan. The

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jaundice is usually reversible on discontinuation of the drug. Subcutaneous injection has resulted in tissue necrosis. Nasal stuffiness may occur. Dry mouth has been reported.

~~LABORATORY TESTS~~ [TEXT RELOCATED TO PRECAUTIONS]
~~The following laboratory tests may be affected in patients who are receiving therapy with promethazine hydrochloride:~~

~~Pregnancy Tests—Diagnostic pregnancy tests based on immunological reactions between HCG and anti-HCG may result in false-negative or false-positive interpretations.~~

~~Glucose Tolerance Test - An increase in glucose tolerance has been reported in patients receiving promethazine hydrochloride.~~

Paradoxical Reactions (Overdosage)
Hyperexcitability and abnormal movements, which have been reported in ~~children~~ pediatric patients following a single administration of ~~promethazine~~ Phenergan Injection, may be manifestations of relative overdosage, in which case, consideration should be given to the discontinuation of the ~~promethazine~~ Phenergan Injection and to the use of other drugs. Respiratory depression, nightmares, delirium, and agitated behavior have also been reported in some of these patients.

~~Management of~~ OVERDOSAGE
Signs and symptoms of overdosage range from mild depression of the central nervous system and cardiovascular system to profound hypotension, respiratory depression, and unconsciousness.

Stimulation may be evident, especially in ~~children~~ pediatric patients and geriatric patients. Convulsions may rarely occur. A paradoxical reaction has been reported in pediatric patients receiving single doses of 75 mg to 125 mg orally, characterized by hyperexcitability and nightmares.

Atropine-like signs and symptoms – dry mouth, fixed, dilated pupils, flushing, etc., as well as gastrointestinal symptoms, may occur.

~~Treatment~~
~~The~~ Treatment of overdosage is essentially symptomatic and supportive. ~~Early gastric lavage may be beneficial if promethazine has been taken orally. Centrally acting emetics are of little use.~~ Only in cases of extreme overdosage or individual sensitivity do vital signs, including respiration, pulse, blood pressure, temperature, and EKG, need to be monitored. Attention should be given to the reestablishment of adequate respiratory exchange through provision of a patent airway and institution of assisted or controlled ventilation. Diazepam may be used to control convulsions. Acidosis and electrolyte losses should be corrected. Note that any depressant effects of Phenergan Injection are not reversed by naloxone.

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Avoid analeptics, which may cause convulsions. ~~Severe hypotension usually responds to the administration of levarterenol or phenylephrine.~~ The treatment of choice for resulting hypotension is administration of intravenous fluids, accompanied by repositioning if indicated. In the event that vasopressors are considered for the management of severe hypotension which does not respond to intravenous fluids and repositioning, the administration of levarterenol or phenylephrine should be considered. EPINEPHRINE SHOULD NOT BE USED, since its use in a patient with partial adrenergic ~~blockage~~ blockade may further lower the blood pressure. Extrapyramidal reactions may be treated with anticholinergic antiparkinson agents, diphenhydramine, or barbiturates. ~~Additional measures include~~ Oxygen may also be administered; ~~and intravenous fluids.~~ Limited experience with dialysis indicates that it is not helpful.

DOSAGE AND ADMINISTRATION

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Do not use Phenergan Injection if solution has developed color or contains precipitate.

To avoid the possibility of physical and/or chemical incompatibility, consult specialized literature before diluting with any injectable solution or combining with any other medication. Do not use if there is a precipitate or any sign of incompatibility.

Important Notes on Administration

The preferred parenteral route of administration for ~~promethazine hydrochloride~~ Phenergan Injection is by deep intramuscular injection. The proper intravenous administration of this product is well tolerated, but use of this route is not without some hazard. Not for subcutaneous administration!

INADVERTENT INTRA-ARTERIAL INJECTION CAN RESULT IN GANGRENE OF THE AFFECTED EXTREMITY (see "WARNINGS—Inadvertent Intra-arterial Injection"). SUBCUTANEOUS INJECTION IS CONTRAINDICATED, AS IT MAY RESULT IN TISSUE NECROSIS (see "CONTRAINDICATIONS").

Injection into or near a nerve may result in permanent tissue damage.

When used intravenously, ~~promethazine hydrochloride~~ Phenergan Injection should be given in concentration no greater than 25 mg/mL at a rate not to exceed 25 mg per minute; it is preferable to inject through the tubing of an intravenous infusion set that is known to be functioning satisfactorily.

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The TUBEX® BLUNT POINTE™ Sterile Cartridge Unit is suitable for substances to be administered intravenously only. It is intended for use with injection sets specifically manufactured as "needle-less" injection systems. As of the date of this circular, the TUBEX BLUNT POINTE is compatible with LifeShield® Prepierced Reseal injection site, Inter-Link® Injection Site, SafeLine® Injection Site, User-Gard® Intermittent Injection Cap, and SafSite® reflux valve*.

The TUBEX® Sterile Cartridge-Needle Unit is suitable for substances to be administered intravenously or intramuscularly.

Allergic Conditions
The average adult dose is 25 mg. This dose may be repeated within two hours if necessary, but continued therapy, if indicated, should be via the oral route as soon as existing circumstances permit. After initiation of treatment, dosage should be adjusted to the smallest amount adequate to relieve symptoms. The average adult dose for amelioration of allergic reactions to blood or plasma is 25 mg.

Sedation
In hospitalized adult patients, nighttime sedation may be achieved by a dose of 25 to 50 mg of ~~promethazine hydrochloride~~ Phenergan Injection.

Nausea and Vomiting
For control of nausea and vomiting, the usual adult dose is 12.5 to 25 mg, not to be repeated more frequently than every four hours. When used for control of postoperative nausea and vomiting, the medication may be administered either intramuscularly or intravenously and dosage of analgesics and barbiturates reduced accordingly.

Preoperative and Postoperative Use
As an adjunct to preoperative or postoperative medication, 25 to 50 mg of ~~promethazine hydrochloride~~ Phenergan Injection in adults may be combined with appropriately reduced doses of analgesics and atropine-like drugs as desired. Dosage of concomitant analgesic or hypnotic medication should be reduced accordingly.

Obstetrics
Phenergan Injection in doses of 50 mg will provide sedation and relieve apprehension in the early stages of labor. When labor is definitely established, 25 to 75 mg (average dose, 50 mg) ~~promethazine hydrochloride~~ Phenergan Injection may be given intramuscularly or intravenously with an appropriately reduced dose of any desired narcotic. ~~Amnesic agents may be administered as necessary~~: If necessary, Phenergan Injection with a reduced dose of analgesic may be repeated once or twice at four-hour intervals in the course of a normal labor. A maximum total dose of 100 mg of Phenergan Injection may be administered during a 24-hour period to patients in labor.

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~~CHILDREN~~ **Pediatric Patients**
Phenergan Injection is not recommended for use in pediatric patients less than two years of age.

In ~~children under the age of 12 years~~ pediatric patients 2 years of age and older, the dosage should not exceed half that of the suggested adult dose. As an adjunct to premedication, the suggested dose is 0.5 mg per lb. of body weight in combination with an equal dose of narcotic or barbiturate and the appropriate dose of an atropine-like drug. Antiemetics should not be used in vomiting of unknown etiology in children pediatric patients (see "WARNINGS—Use in **Pediatric Patients**").

HOW SUPPLIED
Phenergan® (promethazine HCl) Injection is available in the following dosage strengths in **TUBEX® BLUNT POINTE™** Sterile Cartridge Units and Sterile Cartridge-Needle Units, packaged in boxes of 10 **TUBEX®** as follows:

25 mg per mL, NDC 0008-0416-50, 1 mL size **BLUNT POINTE™**.
25 mg per mL, NDC 0008-0416-01, 1 mL size (22 gauge x 1-1/4 inch needle).
50 mg per mL, NDC 0008-0417-01, 1 mL size (22 gauge x 1-1/4 inch needle).

TUBEX® BLUNT POINTE™ Sterile Cartridge Units and Sterile Cartride-Needle Units are intended for use with the **TUBEX®** Injector, which is a reusable plastic injector designed for administration of these products.

Store at room temperature, between 15°C-25°C (59°F-77°F).
Protect from light. ~~Use carton to protect contents from light.~~ Keep covered in carton until time of use.
Do not use if solution ~~is discolored~~ has developed color or contains a precipitate.

Also Available:
Phenergan Injection is also available in 1-mL ampuls ~~of 1 mL~~, in packages of 25 ampuls, as follows:

25 mg per mL, NDC 0008-0063-01.
50 mg per mL, NDC 0008-0746-01.

* * *

LETTER FROM FDA TO WYETH DATED SEPTEMBER 18, 1998 (DEFENDANT'S TRIAL EXHIBIT H)

[logo]

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

Stamp: SEP 18 1998

Stamp: RECEIVED
SEP 25 1998
JOHN SENECA, R. PH.

Stamp: RECEIVED
SEP 25 1998
Nanette E. Holston
U.S. Regulatory Affairs

NDA 8-857/S-009

Wyeth-Ayerst Laboratories
P.O. Box 8299
Philadelphia, PA 19101-8299

Attention: Nanette E. Holston
Manager
U.S. Regulatory Affairs

Dear Ms. Holston:

Please refer to your supplemental new drug application dated September 21, 1981, received September 21,

1981, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Phenergan (promethazine hydrochloride) Injection, 25 and 50 mg/mL.

We acknowledge receipt of your submissions dated May 3, 1988, February 1, March 1, and May 15, 1989, January 7, 1992, August 6, 1996, and May 8 and August 21, 1998. Your submission of May 8, 1998, constituted a full response to our February 21, 1997, action letter.

This supplemental new drug application provides for revised labeling.

We have completed the review of this supplemental application, including the draft package insert dated May 8, 1998, and the final printed carton and container labels dated August 21, 1998, and it is approved effective on the date of this letter.

The final printed labeling (FPL) for the package insert must be identical to the draft package insert submitted May 8, 1998.

Please submit 20 copies of the FPL for the package insert as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement 8-857/S-009." Approval of this submission by FDA is not required before the labeling is used.

If additional information relating to the safety or effectiveness of this drug becomes available before we receive the final printed labeling, revision of the labeling may be required.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

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If you have any questions, contact Mr. David Hilfiker, Project Manager, at (301) 827-1046.

Sincerely yours,

/s/

John K. Jenkins, M.D., F.C.C.P.
Director
Division of Pulmonary Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc: RRA, KFB, VDV, NEH, [illegible], CL, JL, DCM, JPS, JRV, GRO, RA Log

FACSIMILE FROM WYETH TO FDA DATED OCTOBER 23, 1998 (PLAINTIFF'S SUMMARY JUDGMENT EXHIBIT 13)

[handwritten: NDA #8-857]

Wyeth-Ayerst Drug Regulatory Affairs

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DATE:	October 23, 1998
TO:	Mr. David Hilfiker Project Manager Division of Pulmonary Drug Products Food and Drug Administration
FAX:	301-827-1271
FROM:	John Seneca
TELEPHONE:	(610) 902-3724
FACSIMILE:	(610) 964-5972
DEPARTMENT:	U.S. Regulatory Affairs
ADDRESS:	Wyeth-Ayerst St. Davids Center: 170 Radnor-Chester Road, St. Davids PA 19087

NO. OF PAGES (including cover sheet): 1

Dear Mr. Hilfiker:

Reference is made to our approved New Drug Application No. 8-857 for Phenergan® (promethazine) Injection, and to supplement 009, approved on September 18, 1998, which provides for revised labeling.

In preparing the Final Printed Labeling (FPL) for S-009, we have identified a small textual revision that we believe is appropriate for the "Dosage and Administration" section. The revision concerns the third sentence in the "Pediatric Patients" subsection, which currently reads "As an adjunct to premedication, the suggested does is 0.5 mg per lb. of body weight in combination with an equal does of narcotic or barbiturate and the appropriate does of an atropine-like drug." For consistency with the information for adults in the "Preoperative and Postoperative Use" subsection of "Dosage and Administration" and the "Indications" section, which indicate the need for reduced doses of concomitant premedication analgesics, we wish to change the sentence to "As an adjunct to premedication, the suggested dose is 0.5 mg per lb. of body weight in combination with an *appropriately reduced* dose of narcotic or barbiturate and the appropriate dose of an atropine-like drug" (change shown in italics).

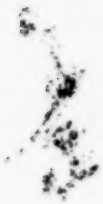
We hope this change will meet with approval for incorporation into the FPL. Please contact me if you have any questions.

Wyeth-Ayerst Laboratories

/s/

John Seneca
Coordinator, U.S. Regulatory Affairs

PHOTOGRAPHS (PAINTIFF'S TRIAL EXHIBITS 37, 39, 40, 41)



PHENERGAN LABELING IN EFFECT IN 2000
(DEFENDANT'S SUMMARY JUDGMENT
EXHIBIT A)

Phenergan®
(promethazine HCl)
Injection
CI 3727-7

Phenergan®

(promethazine HCl)

Injection

DESCRIPTION

Phenergan (promethazine HCl) Injection is a sterile, pyrogen-free solution for deep administration or slow venous administration. Promethazine HCl (10H-phenothiazine-10-ethanamine, N,N,α-trimethyl-monohydrochloride, (±)) is a racemic compound and has the following structural formula:

C17H20N2S • HCl MW=320.89

Each mL of the TUBEX® and RUBY® BLUNT POINTE™ Sterile Cartridge Units contains either 25 or 50 mg promethazine HCl with 0.1 mg edetate disodium, 0.64 mg calcium chloride, not more than 5 mg monothioglycerol, and 5 mg phenol in Water for Injection. The pH range is 4.0 to 5.5. Buffered with sodium potassium acetate and is sealed under nitrogen.

Phenergan (promethazine HCl) Injection is a clear, colorless solution. The product is light sensitive. It should be inspected before use and discarded if either color or particulate is observed.

CLINICAL PHARMACOLOGY

Promethazine HCl is a phenothiazine derivative which possesses antihistaminic, sedative, antiemetic, antimotion sickness, antispasmodic, and anticholinergic effects. Promethazine is a competitive H1 receptor antagonist, but does not block the release of histamine. Structural differences from the neuroleptic phenothiazines result in no neuroleptic (CNS) or hypotensive antagonistic properties. In therapeutic doses, promethazine HCl produces no significant effects on the cardiovascular system. Clinical effects are generally observed within 5 minutes of an intramuscular injection and within 20 minutes of an intravenous injection. Duration of action is four to six hours, although effects may persist up to 12 hours. Promethazine HCl is metabolized in the liver, with the formation of promethazine sulfoxide, N-demethylpromethazine being the predominant metabolite appearing in the urine. Following intravenous administration in healthy volunteers, the plasma half-life for promethazine has been reported to range from 9 to 16 hours. The major plasma half-life for promethazine after intramuscular administration in healthy volunteers has been reported to be 8.8 ± 3.4 hours.

INDICATIONS AND USAGE

Phenergan Injection is indicated for the following conditions:

1. Administration of allergic reactions in blood or plasma.
2. In anaphylaxis, as an adjunct to epinephrine and other standard measures after the acute symptoms have been controlled.
3. For other uncomplicated allergic conditions of the immediate type when oral therapy is impossible or contraindicated.
4. For sedation and relief of apprehension and to produce light sleep from which the patient can be easily aroused.
5. Active treatment of motion sickness.
6. Prevention and control of nausea and vomiting associated with certain types of anesthesia and surgery.
7. As an adjunct to analgesics for the control of postoperative pain.
8. Preoperative, postoperative and obstetric (during labor) sedation.
9. Symptomatic relief of upper respiratory infections, such as nonspecific bronchoconstrictor conditions/ear surgery, and motion sickness, with reduced amounts of respirations or other narcotic analgesics as an adjunct to anesthesia and analgesia.

CONTRAINDICATIONS

Phenergan Injection is contraindicated in comatose states and in persons who have demonstrated an idiosyncrasy or hypersensitivity to promethazine or other phenothiazines.

Under no circumstances should Phenergan Injection be given by intra-arterial injection due to the likelihood of severe complications and the possibility of resultant gangrene (see "WARNINGS—Intra-arterial injection").

Phenergan Injection should not be given by the subcutaneous route; evidence of chemical irritation has been noted, and necrotic lesions have resulted on rare occasions following subcutaneous injection. The preferred parenteral route of administration is by deep intramuscular infusion.

WARNINGS

CNS Depression

Phenergan Injection may impair the mental and physical abilities required for the performance of potentially hazardous tasks, such as driving a vehicle or operating machinery. The impairment may be amplified by concomitant use of other central-nervous-system depressants such as alcohol, sedative-hypnotics (including barbiturates), general anesthetics, narcotics, narcotic analgesics, tranquilizers, etc. (see "PRECAUTIONS—Information for Patients").

Lower Seizure Threshold

Phenergan Injection may lower seizure threshold and should be used with caution in persons with seizure disorders or in persons who are using concomitant medications, such as narcotics or local anesthetics, which may also affect seizure threshold.

Bone-Marrow Depression

Phenergan Injection should be used with caution in patients with bone-marrow depression. Leukopenia and agranulocytosis have been reported, usually when Phenergan has been used in association with other known myelotoxic agents.

Use in Pediatric Patients

PHENERGAN INJECTION IS NOT RECOMMENDED FOR USE IN PEDIATRIC PATIENTS LESS THAN TWO YEARS OF AGE.

CAUTION SHOULD BE EXERCISED WHEN ADMINISTERING PHENERGAN INJECTION TO PEDIATRIC PATIENTS 2 YEARS OF AGE AND OLDER. ANTIEMETICS ARE NOT RECOMMENDED FOR TREATMENT OF UNCOMPLICATED VOMITING IN PEDIATRIC PATIENTS, AND THEIR USE SHOULD BE LIMITED TO PREDUCED VOMITING OF UNKNOWN ETIOLOGY. THE EXTRAPYRAMIDAL SYMPTOMS WHICH CAN OCCUR SECONDARY TO PHENERGAN INJECTION ADMINISTRATION MAY BE CONFUSED WITH THE CNS SIGNS OF UNDIAGNOSED PRIMARY DISEASE, e.g., ENCEPHALOPATHY OR REYE'S SYNDROME. THE USE OF PHENERGAN INJECTION SHOULD BE AVOIDED IN PEDIATRIC PATIENTS WHERE SIGNS AND SYMPTOMS MAY SUGGEST REYE'S SYNDROME OR OTHER HEPATIC DISEASES.

Postoperative large dosages of antihistaminics, including Phenergan Injection, in pediatric patients may cause hallucinations, convulsions, and sudden death. In pediatric patients who are suspected of developing early dehydration, there is an increased susceptibility to dystonias even with the use of Phenergan Injection.

Sulfite-Sensitive Patients

Due to the latent presence of sulfites and ureas in the urine most commonly used for intravenous infusion, extreme care should be exercised to avoid perivascular administration or inadvertent intra-arterial injection. Agents compatible with epinephrine are preferred injection of Phenergan Injection, alone or in conjunction with other drugs intended for intravenous use, suggest that pure, sensitive chemical-sensitive sensory system of blood vessels, and resultant gangrene requiring amputation are likely under such circumstances. Extravascular injection may be minimized if all the above reported side particulars for administration of arterial absorption of the needle is now assessed. There is no proven treatment of management of this condition after it occurs, although sympathetic block and hyperoxygenation are commonly employed during the acute management because of the rapidity of arterial spasm/vessels with other known pharmacological antagonists. Injection of such blood does not preclude vaso-arterial vessels above insult, because blood is destroyed upon contact with Phenergan Injection. Use of cartilage with rigid dilatation or of small bore needles might otherwise have a potential beneficial if this is to not upon done.

When used intravenously Phenergan Injection should be given at a concentration no greater than 25 mg per mL and at a rate not to exceed 25 mg per minute. When administering any potent drug intravenously, it is usually preferable to inject it through the tubing of an intravenous infusion set that is known to be functioning satisfactorily. In the event that a patient complains of pain during intended intravenous injection of Phenergan Injection, the injection should be stopped immediately to permit re-evaluation of possible extravascular placement or perivascular extravasation.

Visual Inspection

This product is light sensitive and should be inspected before use and discarded if either color or particulate is observed.

Other Considerations

Sedative drugs or CNS depressants should be avoided in patients with a history of sleep apnea.

Administration of promethazine has been associated with reported cholestatic jaundice.

PRECAUTIONS

General

Drugs having anticholinergic properties should be used with caution in patients with narrow angle glaucoma, prostatic hypertrophy, stenosing peptic ulcer, pyloroduodenal obstruction and bladder neck obstruction.

Phenergan Injection should be used cautiously in patients with cardiovascular disease or impairment of liver function.

Information for Patients

Phenergan Injection may cause marked drowsiness or impair the mental or physical abilities required for the performance of potentially hazardous tasks, such as driving a vehicle or operating machinery. The use of alcohol, sedative-hypnotics (including barbiturates), general anesthetics, narcotics, narcotic analgesics, tranquilizers, etc. with Phenergan Injection may enhance impairment. Patients' activities should be supervised to avoid potential harm in after-taking or in other hazardous activities.

Patients should be advised to report any involuntary muscle movements.

Persistent or worsening pain or burning at the injection site should be reported immediately.

Avoid prolonged exposure to the sun.

Drug Interactions

CNS Depressants - Phenergan Injection may increase, prolong, or intensify the sedative action of central-nervous-system depressants, such as alcohol, sedative-hypnotics (including barbiturates), general anesthetics, narcotics, narcotic analgesics, tranquilizers, etc. when given concomitantly with Phenergan Injection. The dose of the following should be reduced by at least one half, and the dose of barbiturates should be reduced by one-quarter to one-half. Dosage must be individualized. Excessive amounts of Phenergan Injection initiates by a syncope, may lead to unconsciousness and motor hyperactivity as the patient can pass. Close symptomatic study discussions with addiction control of the pain.

Epinephrine - Although reversal of the vasoconstrictor effect of epinephrine has not been reported with Phenergan Injection, it is recommended that epinephrine NOT be used in the case of Phenergan injection overdose.

Anticholinergics - Concomitant use of other agents with anticholinergic properties should be undertaken with caution.

Monoamine Oxidase Inhibitors (MAOI) - Drug interactions, including an increased incidence of side pharmacological effects, have been reported when some MAOI and phenothiazines are used concomitantly. Although such a reaction has not been reported with Phenergan Injection, the possibility should be considered.

Laboratory Test Interactions

The following laboratory tests may be affected in patients who are receiving therapy with Phenergan Injection:

Pregnancy Tests - Diagnostic pregnancy tests based on immunological reactions between HCG and anti-HCG may result in false-negative or false-positive interpretations.

Glucose Tolerance Test - An increase in glucose tolerance has been reported in patients receiving promethazine HCl.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Long-term animal studies have not been performed to assess the carcinogenic potential of Phenergan Injection, nor are there other animal or human data concerning carcinogenesis, mutagenicity, or impairment of fertility. Phenergan Injection was nonmutagenic in the Ames Salmonella test system.

Pregnancy

Teratogenic Effects—Pregnancy Category C

Teratogenic effects have not been demonstrated in rat feeding studies at doses of 6.25 and 12.5 mg/kg (approximately 2.1 and 4.2 times the maximum recommended human dose, based on Phenergan injection). Fetal doses of 25 mg/kg are spontaneously have been found to produce fetal mortality in rats.

There are no adequate and well-controlled studies of Phenergan Injection in pregnant women. Because animal reproduction studies are not always predictive of human response, Phenergan Injection should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Adequate studies to determine the effect of the drug on perinatal, fetal and development of the prenatal materials have not been conducted.

Nonteratogenic Effects

Phenergan Injection has been reported to have the ability of patients may inhibit platelet aggregation in the newborn.

Labor and Delivery

Phenergan Injection may be used alone or as an adjunct to narcotic analgesics during labor (see "DOSAGE AND ADMINISTRATION"). Limited data suggest that use of Phenergan Injection during labor and delivery does not have an appreciable effect on the duration of labor or delivery and does not contribute the risk of need for intervention in the newborn. The effect on later growth and development of the newborn is unknown. (See also "Nonteratogenic Effects.")

Nursing Mothers

It is not known whether Phenergan Injection is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Phenergan Injection is administered to a nursing woman.

Pediatric Use

Safety and effectiveness in pediatric patients under 2 years of age have not been established.

Phenergan Injection should be used with caution in pediatric patients 2 years of age and older (see "WARNINGS—Use in Pediatric Patients").

Use in Geriatric Patients (approximately 65 years or older)

Since the geriatric responsiveness for sedative drugs tend to be less or greater in patients, the dosage should be reduced for these patients.

ADVERSE REACTIONS

CNS Effects

Drowsiness is the most prominent CNS effect of this drug. Extrapyramidal reactions may occur with high doses. This is dose-related and responsive to a reduction in dosage. Other reported reactions are dizziness, disorientation, confusion, excitation, fatigue, blurred vision, diplopia, tinnitus, vertigo, headache, insomnia, tremors, convulsive seizures, neuroleptic malignant syndrome, hallucinations (daytime and dream), nightmare and hyperreflexia.

Cardiovascular Effects

Tachycardia, bradycardia, faintness, dizziness, and decreases or increases in blood pressure have been reported following the use of Phenergan Injection. Postural hypotension, as the case can also be

PLEASE NOTE: THE WYETH AYERST METAL TUBE/3 HYPODERMIC SYRINGE AND TUBE/3 FAST TRAK SYRINGE HAVE BEEN DISCONTINUED AND REPLACED BY THE TUBEX INJECTOR. EXCHANGE OF THESE DISCONTINUED SYRINGES IS AVAILABLE, FREE OF CHARGE, FROM YOUR WYETH-AYERST SALES REPRESENTATIVE, OR FROM WYETH AYERST DIRECTLY FOR LOADING #1ML (tan) DIATHAL. #INFORMATION ON THESE DISCONTINUED SYRINGES, CONTACT THE MEDICAL AFFAIRS DEPARTMENT AT WYETH AYERST LABORATORIES, P.O. BOX 8299, PHILADELPHIA, PA 19101

TUBEX® Injector

NOTE: The TUBEX Injector is #REUSABLE. do not discard.

TUBEX Sterile Cartridge Needle Unit
DIRECTIONS FOR USE:

TUBEX® BLUNT POINTE™ Sterile Cartridge Unit
DIRECTIONS FOR USE.

TUBEX BLUNT POINTE Sterile Cartridge Unit is intended for use with injection units specifically manufactured as "needle-less" injection systems. As of the date of this circular TUBEX BLUNT POINTE Sterile Cartridge Unit is compatible with LectaShot® Preparated Reveal injection site, SmartJet® Injection Site, Solo-Cart® Injection Site, Uno-Cart® interventus injection Cap, and SoftJet® reflex valve.

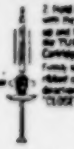
Consult manufacturer's recommendations regarding "Directions for Use" of the "needle less" injection system.

#FOR THE ASEPTIC TECHNIQUE FOR ALL MANIPULATIONS OF STERILE PARTS.

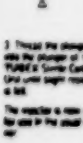
To load a TUBEX Sterile Cartridge Unit into the TUBEX injector

1. Turn the ribbed collar to the "OPEN" position until it stops.

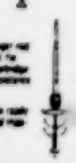
TUBEX Sterile Cartridge Needle Unit



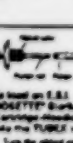
TUBEX BLUNT POINTE Sterile Cartridge Unit



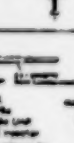
2. Hold the injector with the clear grip end fully down and TUBE/3 Sterile Cartridge Unit firmly against the ribbed collar in the direction of the "CLOSE" arrow.



3. Thread the plunger rod onto the plunger of the TUBEX Sterile Cartridge Unit until slight resistance is felt.

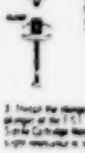


The injection is now ready for use in the usual manner.

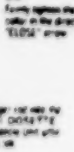


To load an E.S.I. DOSETTE® Sterile Cartridge-Needle Unit into the TUBEX injector

1. Turn the ribbed collar to the "OPEN" position until it stops.

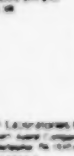


2. Hold the injector with the clear grip end fully down and E.S.I. DOSETTE Sterile Cartridge Needle Unit firmly against the ribbed collar in the direction of the "CLOSE" arrow.



3. Thread the plunger rod onto the plunger of the E.S.I. DOSETTE Sterile Cartridge Needle Unit until slight resistance is felt.

The injection is now ready for use in the usual manner.



4. Engage the needle cap assembly by pulling the cap down over the sterile cartridge hub. The needle is fully engaged when the outer hub is completely covered.

The injection is now ready for use in the usual manner.

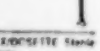
To administer TUBE 3/DOSETTE Sterile Cartridge Needle Units:

Method of administration is the same as with conventional syringe. Remove needle cover by grasping it securely in one hand and pull. Immediately engage needle cover with other hand. ADVICE by barring both rigidly on the plunger and inject.

To administer TUBEX BLUNT POINTE Sterile Cartridge Units:

"Needle less" IV

For administration of a syringe to patient or infusion set with Luer adapter (female)



Remove rubber cover by grasping it securely in one hand and pull. The SoftJet® (tan) sheet over needle. Hold the Luer slip fitting of the TUBEX BLUNT POINTE sterile cartridge to patient line with a gentle, individually engaged twisting motion. Immediately engage needle cover with other hand. Immediately wipe the Luer slip fitting of the TUBEX BLUNT POINTE sterile cartridge to patient line with a gentle, individually engaged twisting motion. Immediately engage needle cover with other hand. ADVICE by barring both rigidly on the plunger and inject.

To administer TUBEX BLUNT POINTE Sterile Cartridge Units

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(17)

No. 06-1249

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IN THE

Supreme Court of the United States

WYETH,

Petitioner,

v.

DIANA LEVINE,

Respondent.

ON WRIT OF CERTIORARI TO
THE VERMONT SUPREME COURT

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QUESTION PRESENTED

Whether the prescription drug labeling judgments imposed on manufacturers by the Food and Drug Administration ("FDA") pursuant to FDA's comprehensive safety and efficacy authority under the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 301 *et seq.*, preempt state-law product liability claims premised on the theory that different labeling judgments were necessary to make drugs reasonably safe for use.

PARTIES TO THE PROCEEDING

Petitioner Wyeth was the defendant and appellant in the courts below. Respondent Diana Levine was the plaintiff and appellee in the courts below.

CORPORATE DISCLOSURE STATEMENT

Petitioner Wyeth has no parent corporation, and no publicly held company owns 10% or more of its stock.

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IN THE

Supreme Court of the United States

No. 06-1249

WYETH,

Petitioner,

v.

DIANA LEVINE,

Respondent.

ON WRIT OF CERTIORARI TO THE VERMONT SUPREME COURT

BRIEF FOR PETITIONER

OPINIONS BELOW

The decision of the Vermont Supreme Court is reported at 944 A.2d 179 (Vt. 2006) (Pet. App. 1a-48a). That court denied Wyeth's motion for reargument in an unreported order (Pet. App. 75a-76a). The trial court's decision denying Wyeth's Motion for Judgment as a Matter of Law (Pet. App. 49a-74a) is unreported.

JURISDICTION

This Court has jurisdiction pursuant to 28 U.S.C. § 1257(a). The Vermont Supreme Court entered its judgment on October 27, 2006 and denied a timely motion for reargument on December 11, 2006. The peti-

tion for writ of certiorari was filed on March 12, 2007 and granted on January 18, 2008.

RELEVANT CONSTITUTIONAL, STATUTORY, AND REGULATORY PROVISIONS

The following constitutional, statutory, and regulatory provisions are set forth in relevant part in the appendix to the petition for writ of certiorari:

- The Supremacy Clause, U.S. Const. art. VI, cl. 2 (Pet. App. 77a);
- Federal Food, Drug, and Cosmetic Act, 21 U.S.C. §§ 352, 355, 393 (Pet. App. 78a-111a);
- Drug Amendments of 1962, Pub. L. No. 87-781, § 202, 76 Stat. 780, 793 (Pet. App. 112a);
- 21 C.F.R. § 314.70 (Pet. App. 113a-125a).

PRELIMINARY STATEMENT

The Federal Food, Drug, and Cosmetic Act (FDCA) and its amendments charge the Food and Drug Administration (FDA) to protect and promote the public health by reviewing the safety and efficacy of new prescription drugs before permitting their interstate distribution. FDA review of a New Drug Application requires careful balancing of the benefits offered by the drug against the potential risks that inevitably accompany the use of any prescription medicine. *Cf. Riegel* v. *Medtronic, Inc.*, 128 S. Ct. 999, 1004-1005 (2008) (analyzing analogous approval requirements for medical devices). The authority to control the content of all the information in a drug's labeling is central to FDA's ability to strike that balance. The agency's comprehensive authority over drug labeling enables FDA to manage the risks associated with each drug in a manner that reduces the potential for harm, while en-

suring that the most efficacious treatments remain available to patients who need them.

Carrying out precisely this balancing of risks and benefits, FDA determined that Wyeth's drug Phenergan is safe and effective for use in the treatment of nausea, and it approved labeling for that drug that permitted intravenous injection as an acceptable method of administering the drug. FDA reached and adhered to this conclusion with full knowledge that exposure of arterial blood to Phenergan can result in severe injury, including gangrene, and that intravenous injection—including "IV push" injection—can lead to inadvertent arterial exposure if performed incorrectly. FDA did not direct Wyeth to contraindicate—i.e., eliminate as a permissible method of administration—IV push or other forms of IV injection, but instead chose to preserve the added effectiveness of intravenous administration and manage this known risk by requiring Wyeth to include carefully tailored warnings and instructions on the drug's labeling. Indeed, since at least 1967, FDA has repeatedly reviewed Phenergan's labeling with respect to arterial blood exposure and mandated that Wyeth distribute the drug only under the verbatim labeling approved by FDA. Absent any newly discovered evidence concerning the nature or degree of these risks, any modification by Wyeth of the contents of these warnings would violate the FDCA and FDA's implementing regulations.

In this case, a Vermont jury was nevertheless permitted to find Wyeth liable for failing to change Phenergan's labeling to eliminate IV push injection from the approved methods of administration. The Vermont Supreme Court affirmed that verdict even though the labeling already contained numerous warnings about the risks associated with IV injection of Phenergan,

and even though respondent never showed or even contended that Wyeth had any material new information about those risks that FDA had not already taken into account when it approved Phenergan's labeling. Compliance with the state-law labeling requirements underlying that verdict would require Wyeth to modify Phenergan's FDA-approved labeling in violation of the FDCA. Moreover, enforcement of this state-law duty would nullify the *ex ante* expert and statutorily mandated balancing of therapeutic benefits and safety risks that FDA performed in approving Wyeth's Phenergan labeling. It would substitute the *ex post* judgment of lay jurors whose members consider drug safety through the lens of a single patient's injury, rather than from the perspective of the overall public health, with the countervailing benefits of the drug to the entire potential patient population in mind. Indeed, counsel for respondent expressly invited the jury to override FDA's decision, telling them "[t]he FDA doesn't make the decision, you do." JA 212.

The judgment below, concluding that Phenergan's labeling should have contraindicated a method of administration that FDA had permitted, thus conflicts with the federal regulatory regime under the FDCA in two ways. First, Wyeth could not change Phenergan's labeling to comply with Vermont law without violating federal law. Second, the state-law requirement frustrates both Congress's objective of having an expert agency balance a drug's risks and benefits and FDA's implementation of that objective in the case of Phenergan. In light of this clear conflict, and under this Court's settled Supremacy Clause precedent, respondent's claims are preempted, and the judgment below should be reversed.

STATEMENT OF THE CASE

I. STATUTORY AND REGULATORY FRAMEWORK

A. Evolution Of FDA's Statutory Authority

The statutory regime under which FDA regulates prescription drugs reflects a pervasive and particularized federal role in regulating the safety and effectiveness of their labeled uses. Drug labeling has been subject to federal control since the 1906 enactment of the Pure Food and Drugs Act. Pub. L. No. 59-384, 34 Stat. 768 (1906). The 1906 Act authorized the federal government to seize drugs that were adulterated or misbranded and to prosecute their manufacturers. *Id.* §§ 1, 2, 5, 10. "Misbranded" drugs included drugs with labeling that was "false or misleading in any particular." *Id.* § 8. The Act did not require premarketing approval, but even during this limited early stage of federal supervision, Congress showed concern about disparate state-law labeling standards and an intent to bring about uniform national labeling. *See* H.R. Rep. No. 59-2118, at 4 (1906) (expressing concern regarding "the varying requirements as to standards and labels in different States" for food products); 40 Cong. Rec. 1217 (1906) (statement of Sen. Nelson) ("[T]he bill will, whenever there is a conflict between the State law and this law, leave this law controlling and be the means of equalizing and doing justice to all parts of the country, instead of having the difficulties we now encounter in many of the States.").

Reacting to mounting evidence of drug safety problems, Congress enacted the FDCA in 1938. Pub. L. No. 75-717, 52 Stat. 1040 (1938). The FDCA precluded interstate shipment of a new drug unless FDA determined that the drug was "safe for use under the conditions prescribed, recommended, or suggested in the

proposed labeling thereof," *id.* § 505(a), (d), 52 Stat. at 1052, and it required that the labeling of all drugs provide "adequate directions for use" and "adequate warnings" against unsafe uses and methods of administration, *id.* § 502(f); *see also id.* §§ 201(p), 301(a), 502, 505(a), (d), 52 Stat. at 1041-1042, 1050-1052 (codified as amended at 21 U.S.C. §§ 321(p), 331(a), 352, 355(a), (d)). The statute prohibited manufacturers from distributing a new drug until a New Drug Application (NDA) for that drug was effective, and it required "specimens of the labeling proposed to be used for such drug" to be submitted as a central component of that NDA. *See id.* § 505(a), (b), 52 Stat. at 1052 (codified as amended at 21 U.S.C. § 355(a), (b)). Thus, if a manufacturer altered a drug's labeling without submitting the proposed changes to FDA, the drug would no longer be one for which an NDA was effective, and interstate distribution of the drug would be unlawful and subject to criminal and civil penalties. *See id.* §§ 201(p), 301(a), (d), 302(a), 303(a), 304, 307, 505(a), (d)(1), 52 Stat. at 1041-1046, 1052 (1938) (codified as amended at 21 U.S.C. §§ 321(p), 331(a), (d), 332(a), 333(a), 334, 337, 355(a), (d)).

In 1962, Congress enlarged FDA's authority by requiring the agency to determine that a drug is not only safe, but also effective "under the conditions prescribed, recommended, or suggested in the proposed labeling thereof" before approving it for distribution. Drug Amendments of 1962, Pub. L. No. 87-781, § 102(b), (c), 76 Stat. 780, 781 (codified as amended at 21 U.S.C. § 355(b), (d)). Congress also gave FDA post-approval authority to require manufacturers to submit reports "of data relating to clinical experience," including adverse drug events, to enable FDA to determine whether to withdraw approval under 21 U.S.C. § 355(e)

on the ground that a drug is not safe or effective under labeled conditions of use. *Id.* § 103(a), 76 Stat. at 782-783 (codified as amended at 21 U.S.C. § 355(k)(1)).[1]

Since the 1962 amendments, determination of a drug's safety has thus been "inseparable from consideration of the drug's effectiveness." *See* S. Rep. No. 87-1744, at 15 (1962). With respect to any NDA, FDA must weigh the safety risks associated with a new drug against the therapeutic benefits it offers and strike a balance between those often competing considerations by regulating "the conditions prescribed, recommended, or suggested in the proposed labeling." *See* 21 U.S.C. § 355(d); *see also* 21 C.F.R. § 314.50(d)(5)(viii) (requiring NDAs to include a "summary of the benefits and risks of the drug, including a discussion of why the benefits exceed the risks under the conditions stated in the labeling"); FDA, *Guidance for Industry, Development and Use of Risk Minimization Action Plans* 4 (Mar. 2005), *available at* http://www.fda.gov/cder/guidance/6358fnl.pdf (describing FDA's risk-benefit assessment as measuring whether, under labeled conditions of use, "the clinical significance and probability of [a drug's] beneficial effects outweigh the likelihood and medical importance of its harmful or undesirable effects"). In this way, FDA fulfills its dual mission to "protect the public health" by barring access to unsafe or ineffective drugs, and to "promote the public health"

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[1] With the enactment of the Food and Drug Administration Amendments Act of 2007, Pub. L. No. 110-85, tit. IX, 121 Stat. 823, 922-962, FDA has enhanced authority to require post-approval labeling changes where "new safety information" comes to light. *See, e.g., id.* §§ 901(a), 902(a), 121 Stat. at 922-926, 943 (codified at 21 U.S.C. §§ 352(z), 355(o)(1), (4)).

by ensuring prompt access to effective and beneficial medicines. 21 U.S.C. § 393(b).

B. FDA's Regulation Of Drug Labeling

"Drug labeling serves as the standard under which FDA determines whether a product is safe and effective." 50 Fed. Reg. 7452, 7470 (Feb. 22, 1985).[2] As such, FDA regulation of labeling serves as "[t]he centerpiece of risk management." 71 Fed. Reg. 3922, 3934 (Jan. 24, 2006). FDA-approved drug labeling "communicates to health care practitioners the agency's formal, authoritative conclusions regarding the conditions under which the product can be used safely and effectively." *Id.*

FDA regulates drug labeling both through rules of general applicability promulgated under its broad regulatory authority, *see* 21 U.S.C. § 371(a), and through particularized review of the labeling for each individual drug. Under general FDA regulations, a drug's labeling must include "a summary of the essential scientific information needed for the safe and effective use of the drug." 21 C.F.R. § 201.56(a)(1). Labeling must describe the drug and its clinical pharmacology, its indications and usage, contraindications, warnings, precautions, and instructions on dosage and methods of administration, and those sections must appear in a specified order. *Id.* § 201.56(d)(1), (e)(1). FDA regulations also specifically describe the required content of each of those sections, *id.* §§ 201.57, 201.80, and mandate that

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[2] The term "labeling" means "all labels and other written, printed, or graphic matter (1) upon any article or any of its containers or wrappers, or (2) accompanying such article." 21 U.S.C. § 321(m).

the labeling describe "adverse reactions," "other potential safety hazards," "limitations in use imposed by them," and "steps that should be taken if they occur," *id.* §§ 201.57(c)(6), 201.80(e).

To ensure that these requirements are met, FDA reviews the labeling submitted with each NDA and supplemental NDA as part of the approval process. FDA may approve an NDA only if it finds that the drug is "safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof"; that there is "substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling thereof"; and that the proposed labeling is not "false or misleading in any particular." 21 U.S.C. § 355(d). And FDA may withhold approval until the manufacturer makes any necessary changes to the labeling. 21 C.F.R. § 314.105(b); *see also id.* § 314.110(a). Once FDA approves an NDA, it requires the manufacturer to distribute the drug only under the precise labeling approved in the NDA. *See id.* § 314.105(b) ("[A]pproval will be conditioned upon the applicant incorporating the specified labeling changes exactly as directed, and upon the applicant submitting to FDA a copy of the final printed labeling prior to marketing.").[3]

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[3] Accordingly, upon approving any NDA, FDA instructs the manufacturer that the drug's final printed labeling must match the labeling that was included in the NDA. *See, e.g.*, Letter from Center for Drug Evaluation and Research, FDA, to Idenix Pharms. Inc. approving NDA 22-011 (Tyzeka) (Oct. 25, 2006), *available at* http://www.fda.gov/cder/foi/appletter/2006/022011s000ltr.pdf ("The final printed labeling (FPL) must be identical to the agreed upon enclosed labeling[.]").

The FDCA permits manufacturers to distribute only those drugs that FDA has certified to be safe and effective *under labeled conditions of use*. 21 U.S.C. § 355(a), (b)(1)(F), (c)(1)(A), (d) (emphasis added). Because the FDCA thus prohibits the distribution of drugs for which no application is effective, and because the FDA-approved labeling is a central component of an effective application, a manufacturer may not change a drug's FDA-approved labeling without obtaining FDA's prior approval of a supplemental NDA. *See* 21 U.S.C. § 355(a), (b)(1)(F), (c)(1)(A), (d); *see also* 21 C.F.R. § 314.70(b)(2)(v)(A), (b)(3). A narrow exception to this rule in the FDA regulations permits a manufacturer who has filed a supplemental NDA to implement a labeling change before FDA has acted on the application if the change is intended "[t]o add or strengthen a contraindication, warning, precaution, or adverse reaction," or "[t]o add or strengthen an instruction about dosage and administration that is intended to increase the safe use of the drug product." 21 C.F.R. § 314.70(c)(6)(iii)(A), (C).[4]

This regulation—known as the "changes being effected," or "CBE," regulation—codifies a longstanding FDA policy under which the agency exercises its enforcement discretion not to take action against a manufacturer that modifies a drug's FDA-approved labeling to add or strengthen warnings without prior approval if the change reflects newly discovered risk information.

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[4] FDA regulations also permit manufacturers to make minor editorial changes to a drug's labeling and changes to the labeling's description of the drug or how it is supplied without submitting a supplemental NDA, so long as the manufacturer documents the change in its annual report to FDA. *See* 21 C.F.R. § 314.70(d)(1), (2)(ix), (2)(x).

See 30 Fed. Reg. 993, 993-994 (Jan. 30, 1965); 73 Fed. Reg. 2848, 2848-2849 (proposed Jan. 16, 2008); *see also* U.S. Br. 13 (Dec. 21, 2007) (CBE regulation constitutes a "limited exception" to prior approval requirement only for changes addressing "*newly discovered risks* from the use of [a] drug" (quoting 47 Fed. Reg. 46,622, 46,623 (Oct. 19, 1982)) (emphasis added in U.S. Br.)). FDA retains ultimate authority to approve or disapprove of the labeling change and to take enforcement action against the manufacturer for misbranding if the change "makes the labeling false or misleading." 71 Fed. Reg. at 3934; *see also* 21 C.F.R. § 314.70(c)(7). Thus, "the determination whether labeling revisions are necessary is, in the end, squarely and solely FDA's under the act." 71 Fed. Reg. at 3934.

II. Factual Background

A. FDA's Regulation Of Phenergan's Labeling

This case involves a prescription drug called Phenergan® Injection, or simply "Phenergan," which treats nausea and other ailments.[5] FDA approved Phenergan in 1955. JA 266-267. Since then, with Wyeth's cooperation, FDA has engaged in extended review and regulation of Phenergan's uses and risks and the information in its labeling. Phenergan has been approved as safe and effective when administered by deep intramuscular ("IM") or intravenous ("IV") injection. *See, e.g.*, JA 390. As Phenergan's labeling indicates, IV administration produces clinical effects four times faster than IM administration and is therefore beneficial for patients in need of rapid treatment. *See* JA 390; *see also* JA 40-41,

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[5] Phenergan is Wyeth's brand name for promethazine hydrochloride, a drug sold by several different drug manufacturers.

60-61; *infra* nn. 10, 11. In one method of IV administration, known as "IV push," the drug is injected (or "pushed") by a syringe that is inserted directly into a patient's vein or into the flexible tubing of an infusion set leading to a needle already inserted into a patient's vein. IV administration can also occur through an "IV drip," whereby the drug is introduced into an infusion system consisting of a hanging IV bag of saline solution that drips down a flexible tube from the bag to a needle or catheter inserted into a patient's vein. *See* JA 46-50.

In 1967, Wyeth advised FDA that it had received a report of a patient who developed gangrene requiring amputation when blood in the patient's arteries came into contact with Phenergan. JA 268-269. At that time, the risk associated with arterial blood exposure to Phenergan was already known, and Phenergan's labeling already warned against intra-arterial injection or perivascular extravasation, which could lead to inadvertent arterial exposure. JA 269.[6]

After the 1967 report, FDA worked closely with Wyeth through a series of communications and meetings to refine Phenergan's warnings with respect to IV administration. In 1973, Wyeth filed a supplemental application seeking approval of certain labeling changes. JA 270. By that time, Phenergan's labeling already advised in two places that intramuscular injection was the "preferred parenteral route of administration." *Id.* The "Dosage and Administration" section stated that "proper intravenous administration ... is

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[6] Perivascular extravasation occurs when a drug intended for intravenous administration escapes from the vein into the surrounding tissue, where it may come into contact with arterial blood. Intra-arterial injection is injection directly into an artery.

well tolerated," but warned that use of this route was "not without some hazard" because, as the labeling noted, "gangrene requiring amputation" could result from exposure of arterial blood to Phenergan through inadvertent intra-arterial injection or perivascular extravasation. JA 276, 277. The "Warnings" section further warned that "[d]ue to the close proximity of arteries and veins in the area most commonly used for intravenous injection, extreme care should be exercised," and specified the maximum concentration and rate of injection for IV administration. JA 276. At FDA's request, Wyeth agreed to add a second statement in the "Warnings" section that IV use of Phenergan was "not without hazard." JA 271, 276.

In 1975, FDA undertook further review of the drug and its labeling. *See* JA 280. As part of that review, Wyeth met with FDA officials to discuss inadvertent intra-arterial injection and other risks of Phenergan and thereafter filed a supplemental NDA to revise Phenergan's labeling. *Id.* FDA responded in May 1976 and instructed Wyeth to make several labeling changes, including adding an upper-case warning that "INT[RA-]ARTERIAL INJECTION MAY RESULT IN GANGRENE OF THE AFFECTED EXTREMITY." JA 279-280, 283. FDA also required Wyeth to add an upper-case instruction designed to enhance the safe IV administration of Phenergan: "ASPIRATION OF DARK BLOOD DOES NOT PRECLUDE INTRA-ARTERIAL NEEDLE PLACEMENT AS BLOOD IS DISCOLORED UPON CONTACT WITH PROMETHAZINE." JA 282.[7]

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[7] Ordinarily, aspiration of a small amount of blood back into the needle before injection helps determine whether a needle is in

FDA convened an Advisory Committee meeting in October 1976 at which IV administration of Phenergan and the risks arising from arterial blood exposure were again evaluated. *See* JA 287-296. The Committee—composed primarily of medical doctors and researchers—approved the continued contraindication of intra-arterial injection on Phenergan's labeling, JA 289, and proposed a further warning that "[i]f a Tubex system is used for intravenous injection, the drug should be injected into a satisfactorily functioning intravenous set." JA 294.[8] Notably, however, the Committee did not recommend that FDA require Wyeth to eliminate IV administration, including IV push, from the drug's labeling.

In 1979, FDA issued a final rule requiring wholesale updates to the content and formatting of prescription drug labeling for all drugs subject to an approved NDA. *See* 44 Fed. Reg. 37,434 (June 26, 1979). FDA subsequently made clear that labeling changes made to comply with the new regulations "would be subject to prior approval by FDA following the submission of supplemental applications." 45 Fed. Reg. 32,550, 32,550 (May 16, 1980). When Wyeth submitted proposed labeling changes to comply with FDA's general mandate, it stated in its application that the draft labeling was being "submitted for FDA review and approval before

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an artery or a vein because arterial blood is brighter red than venous blood. *See* JA 47. Contact with Phenergan causes discoloration of the blood, however, which makes aspiration an unreliable method of protecting against intra-arterial injection. JA 282, 390.

[8] The Tubex® system described in Phenergan's labeling is a type of injection set that consists of a single-use cartridge preloaded with a dose of Phenergan and a reusable plastic injector. *See* JA 43, 391.

being put into use; no labeling changes, therefore, are to be made at this time." JA 299.

During its review of Wyeth's supplemental application, FDA informed Wyeth that further revisions to Phenergan's labeling "relative to the recognition and management of unintended intra-arterial injection" were under consideration. JA 307-308. By that time, Phenergan's labeling already advised that "[w]hen administering any irritant drug intravenously, it is usually preferable to inject it through the tubing of an intravenous infusion set that is known to be functioning satisfactorily." JA 324. The labeling also instructed that if a patient complains of pain during IV injection of Phenergan, "the injection should immediately be stopped to provide for evaluation of possible arterial placement or perivascular extravasation." JA 324.

FDA requested several further labeling changes to supplement these statements. JA 309-319. Specifically, FDA instructed Wyeth to revise the existing warning concerning the risk of gangrene from arterial exposure to state that "[t]here are reports of necrosis leading to gangrene, requiring amputation, following injection of [Phenergan]," and to list several instructions for preventing inadvertent intra-arterial injection, including a statement that "[i]njection through a properly running intravenous infusion [set] may enhance the possibility of detecting arterial placement. In addition, this results in delivery of a lower concentration of any arteriolar irritant." JA 311-312. FDA did not withdraw its approval of IV administration of Phenergan or instruct Wyeth to remove IV push administration from the approved methods of administration identified in the labeling.

In 1988, Wyeth submitted a further supplemental application with new proposed labeling that implemented FDA's instructions. *See* JA 334-335. Wyeth's proposal included the following statement: "Injection into an intravenous infusion set that is known to be running properly should decrease the possibility of inadvertently injecting [Phenergan] intra-arterially. In addition, this results in delivery of a lower concentration of any arteriolar irritant." JA 341; *see also* JA 339-340.

In 1997—explaining that it had taken extra time to review Phenergan's proposed labeling changes to ensure that it had "dotted every 'i' and crossed every 't,'" JA 354—FDA ordered Wyeth to make various labeling changes regarding the dosage and administration of Phenergan, JA 355-365, but to "[r]etain verbiage in current label" concerning inadvertent intra-arterial injection, thus rejecting the previously proposed changes, JA 359.[9] Consistent with the FDCA and its implementing regulations, FDA stated that its approval of the supplemental application was contingent on Wyeth implementing these revisions as FDA directed. JA 356, 365. Wyeth accordingly submitted the revised labeling in compliance with FDA's decision, *see* JA 366-380, and FDA approved the revised labeling, JA 381-383. The approval letter advised Wyeth that the final printed labeling "must be identical to the draft package insert" approved in the letter. JA 382.

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[9] FDA identified the "current" labeling as the version Wyeth submitted at FDA's request in August 1996. *See* JA 356 ("current labeling" refers to labeling submitted in August 1996); *see also* JA 346-352 (Wyeth letter to FDA dated August 6, 1996, enclosing then-current labeling).

B. The Labeling In Place When Respondent Was Treated In 2000

As of 2000, following some 45 years of FDA oversight, Phenergan's labeling included repeated, prominent notice—in four separate sections—of the risk of gangrene arising from inadvertent arterial exposure and gave detailed instructions on how to minimize that risk. The "Warnings" section explained:

> Due to the close proximity of arteries and veins in the areas most commonly used for intravenous injection, extreme care should be exercised to avoid perivascular extravasation or inadvertent intra-arterial injection. Reports compatible with inadvertent intra-arterial injection of Phenergan Injection, usually in conjunction with other drugs intended for intravenous use, suggest that pain, severe chemical irritation, severe spasm of distal vessels, and resultant gangrene requiring amputation are likely under such circumstances.

JA 390. The "Adverse Reactions" and "Dosage and Administration" sections each stated in bold, uppercase type: "INTRA-ARTERIAL INJECTION [CAN] RESULT IN GANGRENE OF THE AFFECTED EXTREMITY." JA 391. The "Contraindications" section likewise stated: "Under no circumstances should Phenergan Injection be given by intra-arterial injection due to the likelihood of severe arteriospasm and the possibility of resultant gangrene[.]" JA 390.

To minimize the risk of arterial blood exposure to Phenergan, both the "Contraindications" and "Dosage and Administration" sections advised that "[t]he preferred parenteral route of administration" is "by deep intramuscular injection." JA 390, 391. The labeling

also noted, however, that IV administration was an option, although "not without some hazard." JA 391. To preserve the option of IV administration for those patients who needed it while minimizing the attendant risk, the "Warnings" section instructed:

> When used intravenously, Phenergan Injection should be given in a concentration no greater than 25 mg per mL and at a rate not to exceed 25 mg per minute. When administering any irritant drug intravenously, it is usually preferable to inject it through the tubing of an intravenous infusion set that is known to be functioning satisfactorily.

JA 390. The "Dosage and Administration" section repeated these instructions. JA 391. The "Warnings" section further advised:

> Aspiration of dark blood does not preclude intra-arterial needle placement, because blood is discolored upon contact with Phenergan Injection. Use of syringes with rigid plungers or of small bore needles might obscure typical arterial backflow if this is relied upon alone.

JA 390. This section also instructed that "[i]n the event that a patient complains of pain during intended intravenous injection of Phenergan Injection, the injection should be stopped immediately to provide for evaluation of possible arterial placement or perivascular extravasation." *Id.*

C. Respondent's Treatment With Phenergan

On April 7, 2000, respondent Diana Levine sought treatment at Northeast Washington County Community Health, Inc. (the "Health Center") for a severe migraine headache and associated nausea. JA 18-19, 103;

Pet. App. 2a. Respondent was initially treated with Demerol for the migraine headache and Phenergan for the nausea. JA 19, 38. Both were administered via deep intramuscular injection, the preferred method of administration identified in Phenergan's labeling. *Id.*; Pet. App. 2a.

Respondent returned to the Health Center later that day because she had not obtained effective relief. JA 19, 38-39; Pet. App. 2a. A physician assistant, Jessica Fisch, then administered a second dose of Demerol and Phenergan intravenously by IV push, injecting the medication from a syringe into the tubing of an IV infusion set that led to a needle she had inserted into what she thought was respondent's vein. JA 19, 39, 106.

Fisch testified at trial that she chose to administer the drugs intravenously because the earlier intramuscular injection "hadn't worked at all," and she "felt that in order to give her some relief, that [she] would give it intravenously and try to get it in a more effective and swifter manner." JA 104. Respondent's supervising physician, Dr. John Matthew, testified at trial that IV injection "provides quicker relief" than IM injection and that it would not have been appropriate to administer Phenergan via IM injection once the Demerol was being administered intravenously "[b]ecause the Demerol would be circulating quickly through her brain and potentially causing her to have vomiting while the Phenergan absorbing IM would be slower and delayed so we might have aggravated her nausea and vomiting." JA 41; *see also* JA 40, 60-61.[10]

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[10] Dr. David Greenblatt, a physician and clinical pharmacologist called by the defense, testified that "there are circumstances in which an intramuscular injection is unreliable," including injec-

Although Phenergan's labeling specified a dosage range for nausea of 12.5 to 25 mg, JA 391, Fisch gave respondent a 50 mg dose, *see* JA 105—double the labeled amount. Moreover, Fisch administered the entire 50 mg double dose without pausing, despite respondent's complaints of pain—pain she later described as "one of the most intense pains that [she] had ever felt" to that point, JA 179-181—even though the labeling instructed that IV injection should stop immediately if the patient complains of pain. JA 111, 183, 390. Respondent thereafter developed the symptoms of arterial exposure and gangrene, requiring amputation of her forearm. Pet. App. 2a.

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tions into overweight patients, which may "be injected into fat and be poorly absorbed," and injections into patients who are dehydrated, seriously ill, or suffering from cardiac disease, who may have "poor blood flow to a muscle," which inhibits absorption. JA 200-201. Dr. Thomas Garvey III testified that IV push injection in particular would be appropriate for "[s]omebody who has been vomiting to the point of severe hypobulimia, fluid depletion, veins are very tough to get into" because "[i]f they're vomiting, you want to get in right away, get in, give the drug." JA 195. Dr. Greenblatt further testified:

> [I]t's a judgment that is made by a treating physician who's treating a given patient and, if there is serious distress due to nausea and vomiting, if it won't stop, if the patient is miserable, if the patient is losing fluid and becoming dehydrated and very ill, then the physician in that urgent situation looks at what's available and, with knowing the risks of IV [Phenergan], would nonetheless make a judgment that the benefit to the patient is worthy of accepting that risk.

JA 201.

III. Proceedings Below

A. Trial Court Proceedings

After settling a malpractice suit against Fisch, the Health Center, and the supervising physician, respondent sued Wyeth in a Vermont trial court, alleging state-law claims for inadequate warnings and instructions. Those claims directly challenged FDA's decision to approve labeling that preserved IV administration of Phenergan as an available option for health care providers. The Amended Complaint alleged that Phenergan is

> not reasonably safe for intravenous administration because the foreseeable risks of harm posed by the intravenous administration of the drug are sufficiently great in relation to its foreseeable therapeutic benefits that reasonable health care providers, knowing of such foreseeable risks and benefits, would not prescribe the drug intravenously for any class of patients.

JA 15 (¶ 6).

Respondent tried the case under this theory. During opening statements, respondent's attorney claimed that Wyeth "had the obligation to publish instructions that would prevent this from happening. And there was a simple instruction that they could have written[:] 'Do not use this drug intravenously.' That's what the case is about." JA 32; *see also* JA 31. At trial, respondent's expert, Dr. Matthew, asserted, "I think the drug should be labeled 'Not for IV use.' If it were going to be used IV, I think that it should say that it has to be in a running—established IV running at a certain rate." JA 59; *see also* JA 63. Dr. Matthew also testified that "the instructions and warnings and so forth as they're

printed I think are inadequate, insufficient. I don't think the drug should be used IV." JA 65.

Dr. Harold Green, another of respondent's witnesses, also criticized FDA's approval of Phenergan's labeling, testifying that, in his opinion, "somebody at the FDA made an administrative error and approved it." JA 82. In his view, the drug should not have been approved for intravenous administration. JA 79-80. Respondent's FDA expert similarly "disagree[d] with FDA's conclusions" to approve Phenergan's labeling. JA 98. While acknowledging that "FDA knew about the risks associated with this product," JA 97, he claimed that "the benefits do not outweigh the risks" of Phenergan and that "the labeling was inadequate," JA 99, 100.[11] None of respondent's witnesses, nor her counsel, ever contended that Wyeth had any new information about the risks of Phenergan that FDA had

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[11] Defense expert witnesses, in contrast, testified that FDA's approval decision was correct and medically sound. One expert disagreed that FDA's 1997 letter directing Wyeth to retain the verbiage in the current label "reflect[ed] an administrative error." JA 189-190. Another expert likewise testified that Phenergan's labeling was adequate and "provide[s] enough instruction to physicians or physician's assistants for the safe use of the product." JA 198-199. He disagreed that "the intravenous use of Phenergan should be banned," JA 200, explaining:

> There are clinical situations in which to produce the needed relief . . . IV may be the preferable or the only way it may be administered. There are obvious risks to IV administration and they are extensively and adequately warned against and, if the treating physician decides that the need to produce relief on that patient is urgent, then it's reasonable to give them the drug IV to produce that relief if it's done properly.

Id.

not already considered in approving Phenergan's labeling.

During closing arguments, respondent's counsel again took issue with Phenergan's FDA-approved labeling, arguing that Wyeth "should have pulled their drug ... from intravenous use. At a minimum, they should have required that you use a free-flowing IV." JA 211. He also invited the jury to override FDA's labeling approval decision: "Thank God we don't rely on the FDA to ... make the safe[ty] decision. You will make the decision." *Id.* "The FDA doesn't make the decision, you do." JA 212.

The court's jury instructions likewise invited the jury to disregard FDA's regulatory judgment: "You must decide the extent to which Wyeth should have warned and advised of the risks and injuries which could result from an injection of Phenergan of the type conducted in this case." JA 217. The court reiterated that "[i]t's for you to decide the nature and scope of the warning required," and that "[t]he warning must reasonably advise of the risks and provide adequate instructions to the physician or other medical professional for its safe use." JA 217-218; *see also* JA 220. The jury returned a verdict in favor of respondent and awarded $7.4 million in damages.[12] JA 225-226, 233-235; Pet. App. 3a.

In motions for summary judgment and judgment as a matter of law, Wyeth argued that respondent's claims were preempted. The trial court rejected that argu-

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[12] The judgment was adjusted to $6,774,000 to account for prejudgment interest and the settlement in respondent's prior malpractice suit. JA 236; Pet. App. 3a.

ment, ruling that FDA's regulation of labeling sets only minimum standards and thus cannot conflict with additional state-law labeling requirements, and that the FDA's CBE regulation would have permitted Wyeth to strengthen the warnings on Phenergan's labeling without prior FDA approval. JA 21-23, 247-252.

B. Vermont Supreme Court Appeal

On appeal to the Vermont Supreme Court, Wyeth again contended that respondent's claims were preempted because Wyeth could not comply with both its federal duty to distribute Phenergan only under the precise labeling approved by FDA, which permitted IV push administration, and its Vermont common-law duty to alter that labeling to foreclose IV push. Wyeth further argued that enforcing a state-law requirement that foreclosed a method of administration approved by FDA would obstruct Congress's objective of protecting the public health by having an expert agency balance drug risks and benefits and FDA's specific fulfillment of that objective with respect to Phenergan. Pet. App. 6a, 16a, 18a. The Vermont Supreme Court rejected both arguments and affirmed. Pet. App. 19a, 28a, 34a.

The Vermont Supreme Court first held that it would not be impossible for Wyeth to comply with both federal and state-law labeling duties because FDA approval of a drug's labeling is merely a "first step" that sets minimum safety standards, and the CBE regulation "appears to allow unilateral changes to drug labels whenever the manufacturer believes it will make the product safer." Pet. App. 13a, 15a, 17a. The court gave no weight to the comprehensive and mandatory nature of the FDA labeling regime or to FDA's specific directive to Wyeth to "[r]etain verbiage in current label." It held instead that preemption would operate only if

Wyeth could show that FDA would have rejected the precise labeling change sought by respondent. Pet. App. 17a-19a; *see also* Pet. App. 36a-37a.

The court rejected Wyeth's claim that the state-law duty underlying respondent's suit would obstruct the objectives of FDA's regulatory regime. In the court's view, all such "obstacle" preemption claims were foreclosed by language in the 1962 amendments to the FDCA that limited preemption claims arising from those amendments to cases of "'direct and positive conflict between such amendments and [a] provision of State law.'" Pet. App. 21a (quoting Drug Amendments of 1962, Pub. L. No. 87-781, § 202, 76 Stat. at 793). The court reasoned that "direct and positive conflict[s]" denoted only those conflicts giving rise to "impossibility" preemption and thus "remove[d] from [its] consideration the question of whether common-law tort claims present an obstacle to the purposes and objectives of Congress." Pet. App. 21a; *see also* Pet. App. 21a-24a.

Chief Justice Reiber dissented, concluding that "compliance with state law in this case would require Wyeth to eliminate uses of Phenergan approved by the FDA and required to be included in the Phenergan labeling." Pet. App. 35a. He explained that "FDA clearly addressed the risks attending IV administration of the drug[,] . . . approved IV administration generally, and specifically warned of the dangers of direct IV administration, including inadvertent arterial injection possibly resulting in amputation." Pet. App. 38a. "These assessments are, in fact, the very essence of the FDA's approval and are in furtherance of the federal objective of advancing public health by balancing the risks and benefits of new drugs and facilitating their optimal use." *Id.* A jury's consideration of drug safety "through the lens of a single patient who has already

been catastrophically injured," in contrast, "is virtually guaranteed to provide different conclusions in different courts about what is 'reasonably safe' than the balancing approach taken by the FDA." Pet. App. 48a. He further concluded that respondent sought a labeling change "that would directly contradict language approved and mandated by the FDA," and that the CBE regulation would not have permitted Wyeth to change Phenergan's labeling in the manner respondent sought. Pet. App. 39a-40a.

SUMMARY OF ARGUMENT

It is well established that "state law that conflicts with federal law is without effect." *Cipollone* v. *Liggett Group, Inc.*, 505 U.S. 504, 516 (1992) (internal quotation marks omitted). Respondent's state-law tort claims conflict with the regime Congress established in the FDCA in two ways.

First, it would have been impossible for Wyeth to comply with the purported state-law duty to modify Phenergan's labeling to contraindicate intravenous administration of Phenergan without violating the FDCA. State law conflicts with federal law and is preempted "when compliance with both federal and state regulations is a physical impossibility." *Fidelity Fed. Sav. & Loan Ass'n* v. *de la Cuesta*, 458 U.S. 141, 153 (1982) (internal quotation marks omitted). Under the FDCA, FDA's approval of a drug's labeling is inextricably intertwined with its approval of the drug itself. The approval process requires FDA to determine whether a new drug is safe and effective under the conditions set forth in the labeling. FDA must also determine whether the labeling satisfies the comprehensive and detailed requirements of federal law, and its ultimate approval of a new drug is conditioned on the manufac-

turer's adopting any changes to the labeling exactly as FDA directs. Once approved, therefore, the labeling ordinarily may not be modified without FDA authorization, and Wyeth would have violated the FDCA had it changed Phenergan's labeling in the manner required by respondent's claims.

The Vermont Supreme Court's contrary conclusion rested on an erroneous interpretation of an FDA regulation that governs when labeling changes may be put into temporary effect without prior FDA approval. As properly construed by FDA, that regulation establishes a limited safe harbor from enforcement for manufacturers that implement labeling changes prior to FDA approval when the change reflects newly acquired information about a drug's risks. That reading is supported by the history of the regulation and its relationship to the purposes of the FDCA as a whole; it is also the interpretation that FDA has reasonably advanced. In this case, respondent has never suggested that Wyeth had any new information about the risks of IV administration of Phenergan that would have warranted a change without FDA approval. Rather, when FDA approved the Phenergan labeling that was in place when respondent was injured, it did so with full information about the risks and benefits of the drug, and it instructed Wyeth to use labeling that FDA had concluded best accommodated those risks and benefits. Wyeth was not permitted to depart from FDA's conclusion—as state law would have required—without violating the FDCA and FDA's regulations.

Respondent's claims are also preempted for the independent reason that they "stand[] as an obstacle to the accomplishment and execution of the full purposes and objectives of Congress." *Hines* v. *Davidowitz*, 312 U.S. 52, 67 (1941). In the FDCA, Congress established

a regime in which an expert agency approves a new drug for distribution under specifically reviewed labeling, based on particularized judgments about the relative risks and benefits of that new drug. Those judgments advance the overall public health by recognizing that the benefits of a particular treatment for certain patients can justify the approval of a drug for uses consistent with its labeling even where its use may also present risk of harm. To minimize risk while preserving the availability of beneficial treatments, FDA reviews the warnings and other information on a drug's labeling and seeks to manage the relevant risks by specifying the information it concludes is necessary to advise users how to use the drug safely and effectively. Thus, contrary to the Vermont Supreme Court's conclusion, the regime Congress created does not establish mere minimum safety standards that a State may freely supplement without limit, but strikes a balance between often competing objectives. FDA carried out Congress's intent by approving labeling for Phenergan that recognized IV injection as a permissible option for health care providers in light of its superior efficacy and speed of relief while providing detailed information on the risks of IV injection and how to avoid them.

Vermont law, in contrast, would displace FDA's expert judgment and substitute the verdicts of lay jurors in fifty States who consider drug safety after the fact on a case-by-case basis, focusing on a single patient's catastrophic injury, rather than the potential benefits of the drug to the public as a whole—an approach that inherently will produce risk-averse determinations. Moreover, respondent's state-law claims interfere with FDA's fulfillment of Congress's intent in the case of Phenergan by second-guessing FDA's determination that, with appropriate warnings and in-

structions on the labeling, the benefits of IV administration of Phenergan outweigh the well-known risk of harm. Because recognition of the state tort action in this case would frustrate the purposes of federal law both by substituting the verdicts of lay juries for the expert balancing Congress directed FDA to conduct and by upsetting the particular balance FDA struck with respect to Phenergan, respondent's claims are preempted.

ARGUMENT

Article VI of the Constitution makes "the Laws of the United States . . . the supreme Law of the Land." U.S. Const. art. VI, cl. 2. "[T]he Supremacy Clause invalidates all state laws that conflict or interfere with an Act of Congress." *Rose* v. *Arkansas State Police*, 479 U.S. 1, 3 (1986) (per curiam). Such a conflict arises "when compliance with both federal and state regulations is a physical impossibility," or when "state law stands as an obstacle to the accomplishment and execution of the full purposes and objectives of Congress." *Fidelity Fed. Sav. & Loan Ass'n* v. *de la Cuesta*, 458 U.S. 141, 153 (1982) (internal quotation marks omitted). Respondent's state-law claims present both types of conflict and are therefore preempted.

I. Respondent's Claims Are Preempted Because It Is Impossible For Wyeth To Comply With Both The State-Law Duties Those Claims Impose And Its Federal Labeling Duties

The FDCA required Wyeth to distribute Phenergan only with the labeling that FDA had approved. FDA's CBE regulation did not permit any modification to the labeling in the absence of newly acquired risk information, which did not exist in this case. Vermont

law, by contrast, imposed a tort-law requirement that Wyeth alter that labeling to foreclose IV administration, or at least IV push injection. Because these two commands are irreconcilable, Vermont law must yield.

A. The FDCA And Vermont Law Imposed Irreconcilable Requirements On Wyeth

FDA's approval of a new drug reflects the agency's definitive judgment that a drug is safe and effective under the conditions of use identified in the drug's labeling, and that the drug as so labeled may lawfully be distributed in interstate commerce. Under this regime, Wyeth was required to distribute Phenergan only with the labeling that FDA had approved. Had Wyeth unilaterally altered the labeling to change the warnings with respect to arterial blood exposure or to eliminate IV push as an approved method of administration, it would have been in violation of federal law and subject to enforcement action by FDA for unauthorized distribution or misbranding. *See* 21 U.S.C. §§ 331(a), (d), 333(a), 334(a), 352, 355(a), (d); 21 C.F.R. § 314.105(b).

As discussed, *supra* pp. 8-10, FDA review of a New Drug Application is a rigorous process that focuses on whether the drug is safe and effective under the labeled conditions of use and whether its labeling complies with extensive and detailed regulations. FDA approval of a drug's labeling is thus part and parcel of its approval of the drug itself. Indeed, should FDA find any deficiencies in the proposed labeling during its review of an NDA, FDA will specify exactly how those deficiencies should be corrected; final approval of the NDA is "conditioned upon the applicant incorporating the specified labeling changes exactly as directed." 21 C.F.R. § 314.105(b).

With limited exceptions discussed below, a manufacturer may not make any changes to a drug after it has been approved, including changes in labeling, without submitting a supplemental application and obtaining FDA's prior approval. 21 C.F.R. § 314.70(b)(1), (b)(2)(v)(A), (b)(3). Federal law thus required Wyeth to submit any proposed change in Phenergan's labeling for FDA review and prohibited Wyeth from implementing that change without FDA's approval.

Similar features of FDA's premarket approval of Class III medical devices recently led this Court to find preemption of state-law tort claims in that analogous context. *Riegel* v. *Medtronic, Inc.*, 128 S. Ct. 999 (2008). In *Riegel*, the Court held that once a Class III medical device receives premarket approval, the FDCA (as amended by the Medical Device Amendments of 1976 (MDA)) forbids the manufacturer to make any change without FDA permission, including a change to the approved labeling, that would "affect safety or effectiveness." *Id.* at 1005. Any change must be submitted by supplemental application for FDA approval before implementation. *Id.* The Court thus held that FDA's detailed, individualized review of the safety and effectiveness of each Class III medical device imposed a federal-law "requirement" that approved devices be made "with almost no deviations from the specifications in its approval application," and preempted conflicting state-law requirements applicable to the device. *Id.* at 1006-1007.

The same holds true for prescription drugs, which are subject to an approval process that is closely similar

to the MDA's premarket approval process.[13] For both drugs and Class III devices, manufacturers must submit full reports of investigations showing whether the product is safe and effective as well as specimens of the proposed labeling. *Compare* 21 U.S.C. § 355(b)(1) (drugs) *with id.* § 360e(c)(1) (devices). In both instances, FDA conducts a detailed, individualized review of the product and is required to deny approval if that product has not been shown to be safe and effective for "use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof." *Compare id.* § 355(d) (drugs) *with id.* § 360e(d)(2) (devices). And in both instances, the manufacturer may not make "changes in labeling" without first submitting a supplemental application and obtaining FDA approval, except under narrow circumstances not implicated here. *Compare* 21 C.F.R. § 314.70(b)(1), (b)(2)(v)(A), (b)(3), (c)(6)(iii) (drugs) *with id.* § 814.39(a)(2), (d)(1), (d)(2)(i)-(iii) (devices).[14]

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[13] Indeed, the premarket approval process for medical devices was modeled on the NDA process for approval of new drugs. *See* H.R. Rep. No. 94-853, at 16 (1976) (FDA authority to regulate safety and effectiveness of devices "is derived from drug law"); *id.* at 17 (standard for determining effectiveness of devices is "derived from existing provisions of the [FDCA] relating to drugs"); H.R. Conf. Rep. No. 94-1090, at 62 (1976) (placing devices previously regulated as drugs into "comparable regulatory status" under device law); 21 U.S.C. § 360j(*l*)(3)(A)(ii) ("[R]equirements applicable to [Class III] device[s] before the enactment date under [the NDA provision] shall continue to apply to such device[s]."); *see also* U.S. Br. 9 ("FDA's review of a new drug application is similar to its premarket approval process for Class III medical devices[.]").

[14] Like premarket approval of Class III medical devices, FDA's review of New Drug Applications thus stands in sharp contrast to the "substantial equivalence" review at issue in *Medtronic*,

Federal law thus required Wyeth to distribute Phenergan only with the FDA-approved labeling, which preserved IV injection, including by IV push, as an approved method of administration. Consistent with that requirement, FDA's 1997 letter to Wyeth approving the Phenergan labeling in place at the time of respondent's injury instructed that "[t]he final printed labeling ... must be identical to" the FDA-approved draft version. JA 382.

The Vermont verdict in this case, to the contrary, rested on a state-law duty to change that labeling to eliminate the option of IV administration, or, at a minimum, IV push. No less than a state statute or regulation, this common-law claim is preempted if it imposed a duty that conflicts with federal law. *See Riegel*, 129 S. Ct. at 1007-1008 ("[C]ommon-law liability is premised on the existence of a legal duty, and a tort judgment therefore establishes that the defendant has violated a state-law obligation." (internal quotation marks omitted)); *see also Buckman Co.* v. *Plaintiffs' Legal Comm.*, 531 U.S. 341, 350-353 (2001); *Geier* v. *American Honda Motor Co.*, 529 U.S. 861, 881-886 (2000). Here, Wyeth could not have complied with both its federal and Vermont duties. In these circumstances, the federal duty under the FDCA must prevail. *See, e.g., Crosby* v. *National Foreign Trade Council*, 530 U.S. 363, 372 (2000) ("We will find preemption

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Inc. v. *Lohr*, 518 U.S. 470 (1996), under which FDA enforces only generally applicable labeling requirements that "reflect[] 'entirely generic concerns about device regulation generally'" and involve no device-specific review for safety and efficacy. *See Riegel*, 128 S. Ct. at 1006-1007 (quoting *Lohr*, 518 U.S. at 501).

where it is impossible for a private party to comply with both state and federal law[.]").

B. The Vermont Court Misinterpreted The CBE Regulation

The Vermont Supreme Court conceded that this case might be "very different" if federal law required Wyeth to use only FDA-approved labeling. Pet. App. 10a. It held, however, that FDA's CBE regulation, 21 C.F.R. § 314.70(c)(6)(iii), eliminated the conflict between federal and Vermont law by allowing a manufacturer to make "unilateral changes to drug labels," without obtaining prior approval, "whenever the manufacturer believes it will make the product safer." Pet. App. 13a. This construction of FDA's regulations is wrong. The CBE regulation permits labeling changes only when the change reflects newly discovered information about a drug's safety that was not previously considered by FDA. Because respondent has not shown or even alleged that Wyeth had any such information concerning the risks of IV administration of Phenergan, the CBE regulation would not have permitted Wyeth to make the labeling changes that respondent's tort suit required.

As discussed, Congress required FDA to review individual drug labeling as part of the NDA process and to hold manufacturers to that approved labeling. Congress did this by expressly tying FDA review and approval of a drug to the labeling under which that drug would be distributed and by making the labeling itself a required and central part of the NDA. *See* 21 U.S.C. § 355(a), (b)(1)(F), (c)(1)(A), (d). Allowing a manufacturer to alter that labeling unilaterally in a manner that affects safety or effectiveness—when it has no material new information that was not available to FDA, but

simply disagrees with how FDA exercised its expert judgment with respect to a risk of which it was fully aware—would undermine the core premise upon which FDA approval of the drug is conditioned: the determination that the drug is safe and effective *as labeled*, *id.* § 355(d). Moreover, alteration of labeling departs from the NDA, making the drug an unauthorized "new drug" for which no NDA is effective; its shipment in interstate commerce would therefore be expressly forbidden by the FDCA. *Id.* § 355(a); *see also id.* §§ 321(p), 331(d). As interpreted by the Vermont Supreme Court, the CBE regulation would thus be so inconsistent with the drug approval scheme established by the FDCA that its promulgation would likely lie outside FDA's statutory authority. *Cf. FDA* v. *Brown & Williamson Tobacco Corp.*, 529 U.S. 120, 125 (2000) (FDA "may not exercise its authority in a manner that is inconsistent with the administrative structure that Congress enacted into law" (internal quotation marks omitted)); *Board of Governors of Fed. Reserve Sys.* v. *Dimension Fin. Corp.*, 474 U.S. 361, 374 (1986) (agency's "rulemaking power is limited to adopting regulations to carry into effect the will of Congress as expressed in the statute").

The history of the CBE regulation demonstrates that it was never intended to carry the broad meaning the Vermont Supreme Court attributed to it. The 1938 FDCA made no provision for changes to approved labeling. In 1944, FDA by regulation provided for labeling changes, but made clear that they could be effected only if a manufacturer filed a supplemental application and obtained FDA's approval prior to implementing the change. 9 Fed. Reg. 12,255, 12,256 (Oct. 10, 1944). In 1956, FDA amended the regulation to make the preapproval requirement even more explicit, providing

that "[a] supplemental application should be submitted for any change . . . that may alter . . . the labeling," and that "[i]f a material change is made from the representations in an effective application for a new drug before a supplement is effective for such change, the application may be suspended." 21 Fed. Reg. 5576, 5579 (July 25, 1956). Suspension would prohibit further distribution of the drug in interstate commerce. *See* 21 U.S.C. § 355(a).

To allow labeling changes reflecting new drug safety information to be "placed into effect at the earliest possible time," FDA issued the predecessor to the current CBE regulation in 1965. 30 Fed. Reg. 993 (Jan. 30, 1965). The regulation provided that a manufacturer could submit a supplemental application proposing certain kinds of labeling changes, and then implement those changes without waiting for FDA approval, if the manufacturer notified FDA that the change was being effected and gave a full explanation of the basis for the proposed change. *Id.* at 993-994. Permissible changes included the addition of "additional warning, contraindication, side-effect, and precaution information." *Id.* Although, as FDA made clear, distribution of the drug without prior FDA approval of the labeling change would be unlawful, FDA stated that it would not pursue sanctions against manufacturers who changed labeling only to include new or strengthened cautionary material based on new safety information:

> It will be the policy of the Food and Drug Administration to take no action against a drug or applicant solely because changes of the kinds described in . . . this section are placed in effect by the applicant prior to his receipt of a written notice of approval of the supplemental new-drug application[.]

Id. at 994. The regulation was thus an exercise of FDA's enforcement discretion under the FDCA, intended to enable prompt adoption of changes needed "in the interest of drug safety." *Id.* at 993. FDA warned, however, that nothing in the regulation limited FDA's ultimate authority to suspend or withdraw approval of an NDA or take action against a drug or manufacturer that otherwise violated the FDCA. *Id.* at 994.

In 1982, FDA proposed to revise the CBE regulation into what is effectively its present form. The proposal explained that the regulation applied to changes made "to correct concerns about *newly discovered* risks from the use of the drug" and to "make available important *new information* about the safe use of a drug product." 47 Fed. Reg. 46,622, 46,623, 46,635 (Oct. 19, 1982) (emphases added). All other labeling changes, except minor, editorial revisions, remained subject to the prior approval requirement. *Id.* at 46,635.[15] FDA adopted the revised regulation in 1985. 50 Fed. Reg. 7452, 7498-7499 (Feb. 22, 1985). In promulgating the final CBE rule, FDA explained that the category of labeling changes that could be made without prior FDA approval had to be narrow because "[s]ubstantive changes in labeling ... are more likely than other

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[15] These statements were consistent with FDA's earlier statements about the CBE regulation. Though FDA had said in 1979 that its regulations did not prohibit labeling changes made to add or strengthen warnings without prior FDA approval, 44 Fed. Reg. 37,434, 37,447 (June 26, 1979), it maintained the view at that time that such changes were permissible "whenever possibly harmful adverse effects associated with the use of the drug are discovered," *id.*, suggesting that only changes reflecting newly acquired risk information would be permitted.

changes to affect the agency's previous conclusions about the safety and effectiveness of the drug." *Id.* at 7470.

Consistent with this history, FDA has recently made clear that the CBE regulation provides only a "limited exception" to the general rule requiring prior approval of labeling changes. U.S. Br. 13. As the Solicitor General and FDA have explained, the CBE regulation is properly read to permit labeling changes without prior approval only when the change is "based on material new information—not information that was previously available to FDA, nor even cumulative new information that does not add materially to the information that was previously available to the agency." *Id.* 14. Even then, FDA retains authority to approve or reject the change, and to take enforcement action against any change that results in misbranding. *Id.* at 15. For this reason, "in practice manufacturers typically consult with FDA before making labeling changes" under the CBE regulation. *Id.*

Earlier this year, FDA reaffirmed this interpretation in a proposed rulemaking. 73 Fed. Reg. 2848, 2850 (Jan. 16, 2008) (defining information appropriate for CBE supplement as "data, analyses, or other information not previously submitted to the agency, or submitted within a reasonable time period prior to the CBE supplement, that provides novel information about the product, such as a risk that is different in type or severity than previously known risks about the product"). Reviewing the history of the CBE regulation, FDA stated that its proposal would "codify the agency's longstanding view" on when labeling changes may be effected without prior approval—namely, when necessary "only to reflect newly acquired information." *Id.* at 2848-2850.

FDA's interpretation of its CBE regulation as a limited exception applicable only where newly acquired, scientifically significant information requires an immediate response is "controlling unless plainly erroneous or inconsistent with the regulation." *Auer* v. *Robbins*, 519 U.S. 452, 461 (1997) (internal quotation marks omitted); *see also Federal Express Corp.* v. *Holowecki*, 128 S. Ct. 1147, 1155 (2008) (deferring to agency's "permissible reading" of its own regulation, where regulation's scope was "less than clear"; agency is entitled to deference "when it adopts a reasonable interpretation of regulations it has put in force"). Deference is particularly appropriate here, where the regulation reflects the agency's exercise of specifically delegated discretion to enforce a complex regulatory scheme. *See Heckler* v. *Chaney*, 470 U.S. 821, 835 (1985) (FDCA's enforcement provisions "commit complete discretion to [FDA] to decide how and when they should be exercised"); *see also id.* at 831-832; *Chevron U.S.A. Inc.* v. *Natural Res. Def. Council, Inc.*, 467 U.S. 837, 865 (1984).

In this case, the CBE regulation—properly construed—did not permit Wyeth to deviate from Phenergan's FDA-approved labeling without prior FDA approval. While a different issue might have been presented had Wyeth learned of significant new risk information not presented to FDA, respondent has never suggested that Wyeth acquired any such new information, or that FDA was not already completely aware of all the risks. Indeed, respondent's counsel argued the opposite, stating to the jury that reports of adverse events associated with arterial blood exposure to Phenergan have existed "since at least 1969," and that "these reports are in the FDA database." JA 31. Respondent's expert similarly conceded that "FDA knew

about the risks associated with this product." JA 97. In these circumstances, Wyeth had no good-faith basis to invoke the CBE regulation, and it would have been impossible for Wyeth to comply with the state-law duty underlying respondent's claims by changing Phenergan's labeling to contraindicate use of IV push injection without violating these federal requirements. The claims are therefore preempted.

II. Requiring Wyeth To Comply With A State-Law Duty To Foreclose IV Push Administration Would Obstruct The Purposes And Objectives Of The Act And Its Implementation By FDA

State law is preempted when it "stands as an obstacle to the accomplishment and execution of the full purposes and objectives of Congress." *Hines*, 312 U.S. at 67. In the FDCA, Congress established a drug-approval regime in which an expert scientific agency makes uniform, national judgments about the safety and effectiveness of prescription drugs by balancing therapeutic benefits against safety risks *ex ante*, taking into account the interests of all potential patients. FDA struck precisely that type of balance in approving IV administration of Phenergan and in determining what warnings and instructions were appropriate to manage its associated risks. Vermont, by contrast, seeks to alter that balance by substituting the judgment of lay juries that focus on individual patients' injuries on a case-by-case basis, effectively disregarding the countervailing benefits of the drug to the public as a whole. *See Riegel*, 128 S. Ct. at 1008. The Vermont judgment thus frustrates both Congress's objective of having an expert agency serve as the ultimate regulator of the labeled conditions of use for which a drug is approved and FDA's specific fulfillment of that objective in establishing an elaborate and balanced network

of cautions and instructions on Phenergan's labeling with respect to the risks of IV administration. Respondent's claims are therefore preempted.[16]

A. Congress Mandated FDA To Make Particularized, Labeling-Specific Decisions That Balance Competing Considerations To Advance The Public Health

In determining whether a state law interferes with the full purposes and objectives of Congress, courts consider "the entire scheme of the statute"—its text, its context, and the policies underlying it *Hines*, 312 U.S. at 67 n.20. Here, the regulatory scheme Congress established provides that FDA's drug-approval and labeling decisions must strike a balance between protecting the public from dangerous misuses of drugs and advancing public health by ensuring that beneficial treatments are available to those who need them.

Congress placed responsibility for resolving the tension between these competing objectives in an expert federal agency. In general, FDA regulation serves the dual objectives of protecting the public from dangerous products and promoting public health by facilitating access to beneficial treatments. *See* 21 U.S.C. § 393(b) (requiring FDA to "protect the public health by ensuring that . . . drugs are safe and effective" and to "promote the public health by promptly and efficiently reviewing clinical research and taking appropriate action on the marketing of regulated products in a

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[16] This case does not present the question whether the FDCA preempts claims that do not implicate labeling, such as manufacturing defect claims. Accordingly, Wyeth confines its argument to the preemptive effect of the Act's labeling requirements and FDA's implementation of those requirements.

timely manner"). These objectives are particularly relevant in the context of drug labeling, which serves as the "centerpiece of risk management" and "communicates to health care practitioners the agency's formal, authoritative conclusions regarding the conditions under which the product can be used safely and effectively." 71 Fed. Reg. at 3934.

Labeling decisions require an understanding of what information a physician or other health care provider needs in order to make informed judgments about what course of treatment is appropriate for a particular patient. FDA must take account of the known risks and benefits of each condition of use for which a drug is labeled and carefully regulate that labeling to ensure that it includes the right balance of warnings and instructions that promotes beneficial use of the drug while minimizing associated risks. "[A]dditional requirements for the disclosure of risk information are not necessarily more protective of patients" because "[e]xaggeration of risk could discourage appropriate use of a beneficial drug." 71 Fed. Reg. at 3935.

Congress thus required a scientific review process presided over by an expert agency that assesses the risk-benefit profile of a drug under labeled conditions of use and actively manages that labeling to ensure that it advances the drug's safe and beneficial use.[17] FDA's

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[17] FDA's oversight of prescription drug labeling is thus very different from the role played by the Environmental Protection Agency with respect to pesticide labeling. As this Court explained in *Bates* v. *Dow Agrosciences LLC*, 544 U.S. 431 (2005), although EPA reviews pesticide labels to ensure against misbranding, EPA does not conduct individualized review of the efficacy of individual pesticides or confirm efficacy claims on a pesticide's labeling. *See id.* at 440 ("EPA's approval of a pesticide label does not reflect any

scientific judgment on these issues warrants deference. *See, e.g., Weinberger* v. *Bentex Pharms., Inc.*, 412 U.S. 645, 653-654 (1973) ("[t]he determination whether a drug is generally recognized as safe and effective . . . necessarily implicates complex chemical and pharmacological considerations" and is "peculiarly suited to initial determination by the FDA."); *Nutraceutical Corp.* v. *Von Eschenbach*, 459 F.3d 1033, 1043 (10th Cir. 2006) ("The review of scientific literature is properly in the province of the FDA, to which this Court grants deference based on its expertise."), *cert. denied*, 127 S. Ct. 2295 (2007); *Schering Corp.* v. *FDA*, 51 F.3d 390, 399 (3d Cir. 1995) ("[FDA's] judgments as to what is required to ascertain the safety and efficacy of drugs fall squarely within the ambit of the FDA's expertise and merit deference from us.").

FDA carried out this obligation to balance competing objectives in the specific case of Phenergan. In approving Wyeth's supplemental application in 1997, as it had in its prior Phenergan labeling actions, FDA sought to maximize Phenergan's therapeutic benefit by balancing the well-known and clearly labeled risk of inadvertent arterial exposure against the benefit of more potent and expeditious anti-nausea relief. On the one hand, intravenous injection of Phenergan offers unique benefits relative to other forms of administration and is

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determination on the part of EPA that the pesticide will be efficacious or will not damage crops or cause other property damage." (internal quotation marks omitted)). For example, in the dispute before the Court in *Bates*, "EPA never passed on the accuracy of the statement" in the labeling challenged in that case. *Id.* Under the FDCA, in contrast, a drug's labeling is central to FDA's review of the safety and efficacy of the drug, and FDA carefully monitors the content and format of each drug's labeling.

the most effective medicine for some patients. *See supra* nn. 10, 11; JA 40-41, 104, 194-195, 200-201. On the other hand, there is a risk that human error during IV injection of Phenergan will cause arterial exposure resulting in serious injury to the patient. Rather than require the contraindication of IV administration altogether (or even just IV push), FDA approved labeling that maintained IV injection as an approved method of administration and managed the attendant risk through a carefully tailored set of warnings and instructions. FDA thus concluded that the network of limitations and warnings in Phenergan's labeling appropriately warned users of the serious risks of IV injection—risks of which FDA was fully informed—and provided information on how IV administration could be done safely.

The Vermont Supreme Court thought that the overriding objective of the FDCA was solely to protect consumers from dangerous products, Pet. App. 20a, and that FDA's approval of a drug and its labeling was therefore nothing more than "a first step in the process of warning consumers," Pet. App. 15a. On that view, federal law sets only minimum safety standards that manufacturers may freely supplement with unlimited additional warnings. Pet. App. 20a. The court thus concluded that a state law requiring manufacturers to add further warnings beyond what FDA required, or to contraindicate methods of administration that FDA had approved as safe and effective, poses no problem under the FDCA because such a requirement would serve the same purpose as federal law—namely, to "encourag[e] pharmaceutical companies to alter their drug labels when they are inadequate to protect consumers." Pet. App. 15a.

As an initial matter, that reasoning is wrong in this case because FDA concluded that Phenergan's labeling

was *not* "inadequate to protect consumers." Pet. App. 15a. Rather, FDA's approval of the 1997 supplemental application indicated its determination that Phenergan was safe and effective under the labeled conditions of use, including use by IV injection. 21 U.S.C. § 355(d). More fundamentally, however, the Vermont Supreme Court erred in concluding that Congress's sole objective in the FDCA was to protect consumers from dangerous products, and that federal requirements therefore constitute only minimum safety standards.[18] The regulatory scheme that Congress established in the FDCA and that FDA implemented in the specific case of Phenergan serves competing goals: to protect the public from unreasonable risk of harm, while ensuring the availability of beneficial treatments, all of which carry a certain degree of risk. *See supra* pp. 7-8, 41-42; *see also Riegel*, 128 S. Ct. at 1009. And an approved drug's labeling must provide sufficient instructions for safe and effective use, while avoiding limitations that foreclose beneficial use of a drug in an effort to avoid all risk of human error. For these reasons, as the United States has explained, "'FDA interprets the [FDCA] to establish both a "floor" and a "ceiling"' with respect to drug labeling," U.S. Br. 11 (quoting 71 Fed. Reg. at 3935) (alteration in U.S. Br.), and "FDA's approval of labeling for a new drug reflects FDA's expert judgment that the labeling strikes the appropriate balance,"

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[18] In any event, even if state and federal law share the same ultimate goal, state law is still preempted if it "interferes with the methods by which the federal statute was designed to reach this goal." *International Paper Co.* v. *Ouellette*, 479 U.S. 481, 494 (1987). "The fact of a common end hardly neutralizes conflicting means[.]" *Crosby*, 530 U.S. at 379.

id. The Vermont Supreme Court erred in concluding otherwise.

B. The Vermont Judgment Conflicts With Congress's Public-Health Objectives

Respondent's state-law claims frustrate the public-health objectives underlying the FDCA—and FDA's implementation of the FDCA in the case of Phenergan—by interfering with Congress's purpose to entrust an expert agency to make drug labeling decisions that strike a balance between competing objectives. Pursuant to Congress's mandate, FDA made an expert judgment that the benefits of a speedier and more potent method of administration outweighed the risks associated with IV administration of Phenergan, and that the labeling properly explained the risks and how to avoid them and thus should be retained. FDA based that judgment on its assessment of the overall public health. Under Vermont law as applied below, in contrast, a single lay jury reweighs those risks and benefits, focusing not on the public health as a whole, but on the harm suffered by a single patient. As this Court observed in *Riegel*, a jury "sees only the cost of a more dangerous design, and is not concerned with its benefits; the patients who reaped those benefits are not represented in court." 128 S. Ct. at 1008. As such, juries will be systematically more risk-averse, which can undermine the public health by leading manufacturers to include excessive warnings on labeling or to remove effective methods of administration from the labeling.[19]

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[19] Chief Justice Reiber made a similar point in dissent below, noting that "the jury does not assess reasonableness in the context of public health and the associated risk-benefit analysis," but rather "views the safety of the drug through the lens of a single

This Court has made clear that where federal law strikes a balance between competing objectives, "that is not a judgment the States may second-guess." *Bonito Boats, Inc.* v. *Thunder Craft Boats, Inc.*, 489 U.S. 141, 152 (1989). Rather, state regulation "must yield to the extent that it clashes with the balance struck by Congress." *Id.* Thus, in *Geier* v. *American Honda Motor Co.*, 529 U.S. 861 (2000), this Court held that state tort law was preempted to the extent that it reached a different balance among several competing objectives than the balance the federal policy had struck. *Id.* at 874-881.

This case presents a conflict between state and federal law analogous to the one the Court addressed in *Geier*. The federal safety regulation at issue in *Geier* "deliberately provided the manufacturer with a range of choices among different passive restraint devices," which "would bring about a mix of different devices introduced gradually over time." 529 U.S. at 864-865, 875. The goal of the federal scheme was not to set minimum airbag standards—seeking "the more airbags, and the sooner, the better," *id.* at 874—but to accommodate multiple competing concerns, *id.* at 875. This Court held that the federal objective preempted the alleged tort duty because the duty "would have presented an obstacle to the variety and mix of devices that the federal regulation sought" and "stood as an obstacle to the general passive restraint phase-in that the federal regulation deliberately imposed." *Id.* at 881.

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patient who has already been catastrophically injured," an approach that "is virtually guaranteed to provide different conclusions in different courts about what is 'reasonably safe' than the balancing approach taken by the FDA." Pet. App. 48a.

Here, as in *Geier*, FDA balanced competing concerns of safety and therapeutic benefit by considering the risks of IV administration of Phenergan and preserving the option for physicians to administer Phenergan by IV push in appropriate cases, subject to carefully crafted warnings and instructions in the labeling. Vermont sought to foreclose that option here by basing a damage award on its availability, an award imposed by a lay jury that reconsidered the precise risk information FDA had already weighed. Thus, just as in *Geier*, respondent's claims stand as an obstacle to the accomplishment and execution of federal objectives and are preempted.[20]

In contrast, this Court has rejected preemption claims in cases where federal law did not impose particularized requirements that reflected an accommodation of competing concerns. In *Medtronic, Inc.* v. *Lohr*, 518 U.S. 470 (1996), for example, the Court held that

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[20] *See also Buckman*, 531 U.S. at 348-350 (holding state tort claims challenging manufacturer's fraudulent misrepresentations to FDA to be preempted because they threatened to "skew[]" the "balance sought by [FDA]" in exercising its options to punish and deter fraud and thus would "inevitably conflict" with FDA's statutory responsibilities); *Barnett Bank of Marion County, N.A.* v. *Nelson*, 517 U.S. 25, 31, 37 (1996) (finding preemption where state law prohibited activities that federal law authorized); *Ouellette*, 479 U.S. at 494-497 (state law that "upset[] the balance of public and private interests so carefully addressed" by federal statute and that potentially undermined "Congress's considered judgment as to the best method of serving the public interest and reconciling . . . often competing concerns" was preempted); *de la Cuesta*, 458 U.S. at 156 (by "limiting the availability of an option" the federal agency considered essential to its objectives, state created an "obstacle to the accomplishment and execution of the full purposes and objectives" of federal law (internal quotation marks omitted)).

the "substantial equivalency" regime for FDA approval of certain medical devices did not preempt common-law claims because the approval process reflected only general concerns about device regulation, not particularized determinations about the safety and effectiveness of specific devices. *Id.* at 501. The case was thus "quite unlike a case in which the Federal Government has weighed the competing interests relevant to the particular requirement in question, reached an unambiguous conclusion about how those competing considerations should be resolved in a particular case or set of cases, and implemented that conclusion via a specific mandate on manufacturers or producers." *Id.*[21] FDA's approval of Phenergan's labeling, in contrast, constitutes precisely the kind of case distinguished in *Lohr*: FDA considered and resolved the competing considerations relevant to IV administration of Phenergan and implemented that decision by requiring Wyeth to distribute the drug only with specified labeling.

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[21] *See also Riegel*, 128 S. Ct. at 1006-1007; *supra* n.14. This Court's decision in *Sprietsma* v. *Mercury Marine*, 537 U.S. 51 (2002), is similarly distinguishable. There, the Court found no preemption because the Coast Guard had decided to take no regulatory action at all on the question whether boats should be equipped with propeller guards. Contrary to the federal government's position in *Geier*, the Coast Guard in *Sprietsma* made clear that it perceived no conflict between state-law boat safety requirements and the federal regulatory scheme under the Federal Boat Safety Act, which expressly described the Coast Guard's regulations as setting "minimum safety standards." *Id.* at 58 n.6, 67-68. And unlike FDA's particularized review of each prescription drug it approves, the Coast Guard in *Sprietsma* did not undertake to "certify the acceptability of every recreational boat subject to its jurisdiction." *Id.* at 69.

Consistent with this conclusion, FDA has explained that, in its view, a state-law requirement that a manufacturer include additional warnings, instructions, or other information on a drug's labeling beyond what FDA has required would upset the balance struck under federal law between drug risks and benefits. 71 Fed. Reg. at 3934-3936. By requiring labeling to rule out methods of administration or other uses that FDA has approved, or to include excessive warnings and cautionary material sufficient to appease a risk-averse jury, a state-law duty to warn "can erode and disrupt the careful and truthful representation of benefits and risks that prescribers need to make appropriate judgments about drug use" and "discourage appropriate use of a beneficial drug," thereby "undermining the objectives of the act." *Id.* at 3935.[22] Thus, because respondent's claims frustrate the purpose of the FDCA's labeling requirements and stand as an obstacle to the

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[22] As this Court observed in *Geier*, where Congress has delegated authority to an expert agency to implement a comprehensive regulatory scheme in a technical area, it is appropriate to give weight to the agency's conclusion that state regulation would pose an obstacle to the achievement of federal objectives: "The agency is likely to have a thorough understanding of its own regulation and its objectives and is uniquely qualified to comprehend the likely impact of state requirements." 529 U.S. at 883 (internal quotation marks omitted); *see also Lohr*, 518 U.S. at 496 ("Because the FDA is the federal agency to which Congress has delegated its authority to implement the provisions of the Act, the agency is uniquely qualified to determine whether a particular form of state law stands as an obstacle to the accomplishment and execution of the full purposes and objectives of Congress." (footnote and internal quotation marks omitted)); *Colacicco* v. *Apotex, Inc.*, 521 F.3d 253, 274-276 (3d Cir. 2008) (FDA's view that imposition of liability under state law for failure to warn would interfere with federal regulatory objectives is entitled to deference).

achievement of Congress's objectives, the claims are preempted.[23]

C. The 1962 Amendments To The FDCA Do Not Limit The Application Of This Court's Settled Conflict Preemption Principles

The Vermont Supreme Court rejected Wyeth's argument that respondent's state-law claims present an obstacle to Congress's purposes and objectives on the ground that section 202 of the 1962 Amendments to the FDCA limited the statute's preemptive effect to cases where compliance with both state and federal law was impossible. Pet. App. 21a. Section 202 states:

> Nothing in the amendments made by this Act to the Federal Food, Drug, and Cosmetic Act shall be construed as invalidating any provision of State law . . . unless there is a direct and positive conflict between such amendments and such provision of State law.

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[23] No "presumption against preemption" applies to alter this analysis. Regulation of drug labeling has now been the domain of the federal government for more than a century, and there is no presumption against federal preemption when States regulate in an area where there has been a history of significant federal presence. *United States* v. *Locke*, 529 U.S. 89, 108 (2000); *see also Buckman*, 531 U.S. at 347-348. Even where the presumption does apply, the existence of an actual conflict between federal and state law, even if implied, requires the state law to yield notwithstanding the presumption. *See Felder* v. *Casey*, 487 U.S. 131, 138 (1988) ("'[A]ny state law, however clearly within a State's acknowledged power, which interferes with or is contrary to federal law, must yield.'" (quoting *Free* v. *Bland*, 369 U.S. 663, 666 (1962)); *de la Cuesta*, 458 U.S. at 153 ("The relative importance to the State of its own law is not material when there is a conflict with a valid federal law, for the Framers of our Constitution provided that the federal law must prevail." (internal quotation marks omitted)).

Pub. L. No. 87-781, § 202, 76 Stat. 780, 793 (1962). In the Vermont Supreme Court's view, a "direct and positive conflict" exists only where compliance with both federal and state law is a physical impossibility. Pet. App. 21a-22a. Its rejection of Wyeth's "impossibility" argument was therefore "a complete answer to the question of preemption." Pet. App. 23a. That conclusion was incorrect.

It is far from clear whether section 202 addresses the preemptive scope of any part of the FDCA regime other than "the amendments made by" the 1962 Act. *See* U.S. Br. 16. But even if section 202 is relevant here, it would not preclude preemption in this case, because that section does nothing more than make clear that the FDCA does not occupy the entire field of all matters relating to prescription drugs, a claim that is not implicated here. By using the phrase "direct and positive conflict," Congress endorsed application of conflict preemption principles, using language from this Court's decisions with a well-settled meaning that includes both "impossibility" and "obstacle" conflict preemption. *See, e.g., Sinnot* v. *Davenport*, 63 U.S. (22 How.) 227, 242-243 (1859) (finding "direct and positive" conflict between federal and state licensing provisions despite possibility of dual compliance); *Missouri, Kan. & Tex. Ry. Co.* v. *Haber*, 169 U.S. 613, 623 (1898) (test for "direct and positive conflict" is whether state provisions may "stand without obstructing or embarrassing the execution of the act of Congress"); *see also Phillips* v. *General Fin. Corp. of Fla.*, 297 So. 2d 6, 8 (Fla. 1974) (test for "direct and positive conflict" is "whether the state law frustrates the operation of the federal law and prevents the accomplishment of its purpose"); *Oefinger* v. *Zimmerman*, 601 F. Supp. 405, 412-413 (W.D. Pa. 1984) (analyzing whether "direct and positive conflict"

existed between state law and federal law under principle of "obstacle" conflict preemption), *aff'd*, 779 F.2d 43 (3d Cir. 1985); *Conkle* v. *Wolfe*, 722 N.E.2d 586, 593-594 (Ohio Ct. App. 1998) (same). Indeed, as this Court has explained:

> The Court has not previously driven a legal wedge—only a terminological one—between "conflicts" that prevent or frustrate the accomplishment of a federal objective and "conflicts" that make it "impossible" for private parties to comply with both state and federal law. Rather, it has said that both forms of conflicting state law are "nullified" by the Supremacy Clause, and it has assumed that Congress would not want either kind of conflict.

Geier, 529 U.S. at 873 (citations omitted). The Third Circuit recently confirmed this view, holding that the "direct and positive conflict" provision in section 202 "merely states that conflict preemption applies." *Colacicco* v. *Apotex Inc.*, 521 F.3d 253, 262 n.8 (3d Cir. 2008).

Consistent with this case law, Congress used the term "direct and positive conflict" in the 1962 Amendments not to narrow conflict preemption, but to foreclose claims of "field preemption"—which is not at issue here—and avoid the ouster of non-conflicting state-law requirements based on the comprehensiveness of FDA's authority under the 1962 Amendments. As a sponsor of the Amendments explained:

> [T]here are some confusing decisions of the Court which hold that whenever the Congress enacts a law it preempts jurisdiction over all matter contained in the act to the exclusion of all State laws. . . . This would merely say that

> this Food and Drug Act shall not be construed as the intent of Congress to abolish all State laws on the same subject where they are not in conflict with the Federal law.

108 Cong. Rec. 21,083 (1962) (statement of Rep. Smith). That was consistent with a then-recent Supreme Court decision that used the phrase "direct and positive" to distinguish conflict preemption from field preemption. *See United Constr. Workers* v. *Laburnum Constr. Corp.*, 347 U.S. 656, 663 & n.5 (1954).[24]

In sum, section 202 does not support the implausible conclusion that Congress would tolerate an actual conflict between state and federal law that defeats the purposes of its own legislation and upsets the carefully crafted balance Congress and FDA have reached between the competing objectives of maximizing safety and maximizing therapeutic benefit. Such a conflict exists here. Respondent's claims are therefore preempted.

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[24] The Vermont Supreme Court relied solely on the Fourth Circuit's decision in *Southern Blasting Services, Inc.* v. *Wilkes County, North Carolina*, 288 F.3d 584 (4th Cir. 2002). But that decision merely held that a preemption clause requiring "direct and positive conflict" signified only that "Congress did not intend to occupy the field" and "simply restates the principle that state law is superseded in cases of an actual conflict with federal law." *Id.* at 590-591. Although the court recited only the "impossibility" prong of the conflict preemption standard, *id.* at 591, it in fact went on to consider whether the local ordinances at issue could be reconciled with congressional purposes and objectives—the essence of an "obstacle" conflict preemption analysis. *Id.* at 592.

CONCLUSION

The judgment of the Vermont Supreme Court should be reversed.

Respectfully submitted.

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Supreme Court of the United States

WYETH,
Petitioner,

v.

DIANA LEVINE,
Respondent.

On Writ of Certiorari to the Supreme Court of Vermont

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QUESTION PRESENTED

Whether Food and Drug Administration ("FDA") approval of a prescription drug's labeling preempts state-law failure-to-warn claims in the absence of any express preemption provision in the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 301 *et seq.*, or any evidence that FDA considered the risks and benefits of the specific method of administering the drug that caused the injuries upon which the state-law claim is premised.

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INTRODUCTION

For more than a century, patients injured by dangerous drugs have successfully brought state-law failure-to-warn claims against drug manufacturers. Aware of those state-law remedies, Congress did not include an express preemption provision in the Federal Food, Drug, and Cosmetic Act ("FDCA"), 21 U.S.C. § 301 *et seq.* Nor has it ever added a preemption clause for prescription drugs in numerous statutory amendments to the FDCA, even as it enacted an express preemption provision for medical devices. *See Riegel v. Medtronic, Inc.*, 128 S. Ct. 999, 1009 (2008).

Until 2002, the Food and Drug Administration ("FDA") viewed such state-law failure-to-warn claims as complementing federal regulatory efforts by bringing to light drug risks unknown or underappreciated by FDA. Until the 1990s, drug companies rarely invoked preemption, because a widely recognized state-law regulatory-compliance defense enabled defendants to avoid liability when the agency's action disproved negligence.

In this case, Diana Levine's arm was amputated after she developed gangrene from an injection of Wyeth's anti-nausea drug Phenergan. The record established that the intravenous push method used to inject the drug directly into Ms. Levine's arm ("IV push") significantly increased the risks of arterial exposure to Phenergan, which causes gangrene, without providing any countervailing benefit. The evidence further showed Ms. Levine could have received the drug's benefit with virtually no risk of arterial exposure had the drug been administered in other, safer ways. Consistent with the FDCA's misbranding provision, which requires drug labeling to

contain "adequate warnings" against "unsafe dosage or methods or duration of administration or application," 21 U.S.C. § 352(f), the Vermont courts found that Wyeth's failure to warn of the greater risks of IV-push administration of Phenergan, or to instruct clinicians not to use that method of administration, violated a state-law duty to warn.

In asserting preemption, Wyeth claims (at 28) that FDA makes "particularized judgments about the relative risks and benefits" of drugs and their labeling. Contrary to that rhetoric, Wyeth produced no evidence below showing that it ever submitted for FDA consideration, or that the agency performed on its own, a balancing of particularized risks and benefits of IV-push injection versus other forms of administration. Wyeth's claim of conflict preemption, therefore, rests not on any specific conflict between a particular conclusion reached in reviewing the Phenergan labeling and state-law duties to warn, but rather on the mere fact that FDA approved the Phenergan labeling and authorized Wyeth to market the drug. If accepted by this Court, that position would radically change the traditional state-law remedial process that has developed over the past century with congressional acceptance.

In an about-face from the position it had taken since the FDCA's enactment, FDA unconvincingly supports preemption in this case. It offers a never-before-advanced approach to preemption (which Wyeth itself does not advocate), suggesting that failure-to-warn claims should be preempted where FDA has received information about the general risks at issue. That approach, however, would inoculate manufacturers from liability when they advise FDA of side effects without informing physicians of the

significantly greater risks of causing those effects by administering the drug one way instead of through other, safer methods.

This case does not involve a life-saving, but risky, drug made available following full weighing of risks and benefits by FDA and full disclosure to health-care professionals. Rather, it concerns whether a drug manufacturer may be held liable under state law for inadequately warning that one method of administering an anti-nausea drug causes unacceptable risks of amputation. When neither Wyeth nor FDA performed any risk-benefit analysis of different ways of administering Phenergan, preemption simply provides a windfall for the drug maker. It decreases manufacturers' incentives to improve safety and to inform FDA of risks, impedes FDA's ability to protect consumers, and denies compensation to victims of dangerous drugs for catastrophic but avoidable injuries.

STATEMENT

A. Statutory and Regulatory Background

1. In the nineteenth and early twentieth centuries, centralized markets for food and drugs developed to serve growing urban centers. *See* Peter Barton Hutt et al., *Food and Drug Law* 7 (3d ed. 2007) ("*Food and Drug Law*"). Courts routinely recognized failure-to-warn claims and other causes of action for consumers injured by dangerous drugs.[1] Such actions had their roots in cases from "the early days of the common law," when "those engaged in the business of selling

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[1] *See, e.g.*, *Halloran v. Parke, Davis & Co.*, 280 N.Y.S. 58, 59 (App. Div. 1935) (per curiam); *Blood Balm Co. v. Cooper*, 10 S.E. 118, 119 (Ga. 1889); *Fisher v. Golladay*, 38 Mo. App. 531, 1889 WL 174, at *3-*6 (1889); *Thomas v. Winchester*, 6 N.Y. 397, 407-10 (1852); *Fleet v. Hollenkemp*, 52 Ky. 219, 1852 WL 1716, at *5-*6 (1852).

food intended for human consumption" were first "held to a high degree of responsibility for their products." *Restatement (Second) of Torts* § 402A cmt. b (1965).

Against that backdrop of common-law liability, Congress in 1938 enacted the FDCA "for the purposes of safeguarding the public health [and] preventing deceit upon the purchasing public." H.R. Rep. No. 75-2139, at 3 (1938). The Act's "high purpose" was "to protect consumers." *Kordel v. United States*, 335 U.S. 345, 349 (1948); *see also United States v. Dotterweich*, 320 U.S. 277, 280, 282 (1943) (FDCA protects the health and safety of consumers, which, "in the circumstances of modern industrialism, are largely beyond self-protection"). It required manufacturers for the first time to submit to federal safety review before marketing drugs. *See* FDCA § 505, 52 Stat. 1052-53.

A fundamental provision of the FDCA – then, as now – prohibits selling misbranded or adulterated products in interstate commerce. *See id.* §§ 301(a)-(c), 501-502, 52 Stat. 1042, 1049-51 (codified as amended at 21 U.S.C. §§ 331(a)-(c), 351-352). An early version of the bill that became the FDCA included a federal private right of action for injured consumers. *See* H.R. 6110, 73d Cong. § 25 (1933). Witnesses testified that the provision was unnecessary because long-standing state-law remedies protected consumers,[2] and Congress omitted it from the enacted legislation.

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[2] *See, e.g., Food, Drugs, and Cosmetics: Hearings on S. 1944 Before a Subcomm. of the S. Comm. on Commerce*, 73d Cong. 400 (1933) (statement of W.A. Hines) (recommending federal right of action "be stricken from the bill on the ground that it is unnecessary" because "common-law right of action exists"); *id.* at 403 (statement of J.A. Ladds) ("This act should not attempt

2. When Wyeth's application to market Phenergan became effective in 1955 (JA267), the FDCA prohibited selling in interstate commerce a "new drug" – one not generally recognized by experts as safe for its intended use, *see* 21 U.S.C. § 321(p) (1952) – unless "an application" filed under the Act was "effective with respect to such drug." *Id.* § 355(a). Applicants had to submit reports of investigations and other materials "to show whether or not such drug is safe for use," as well as "specimens of the labeling proposed to be used for such drug." *Id.* § 355(b). FDA could "issue an order refusing to permit the application to become effective" only if the drug had not been shown to be "safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling." *Id.* § 355(d).

If FDA failed to act, the application typically became effective 60 days after filing. *Id.* § 355(c). Subsequently, FDA could suspend the application's effectiveness if it found the drug unsafe or the application contained a material misstatement. *Id.* § 355(e). The FDCA provided for judicial review of an FDA order "refusing to permit [an] application to become effective, or suspending the effectiveness of the application," but not where FDA permitted an application to become effective. *Id.* § 355(h). Indeed, Congress has never authorized judicial review of FDA approval of a new-drug application. By contrast, in 1976, Congress provided for judicial review of the approval of an application to market a medical device. *Compare id. with* 21 U.S.C. § 360g(a)(4).

When Congress passed the Drug Amendments of 1962 ("1962 Amendments"), it required for the first

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to modify or restate the common law with respect to personal injuries.").

time that "new drugs meet an additional test of 'effectiveness' in addition to the existing test of 'safety.'" S. Rep. No. 87-1744, at 9-10 (1962). Whereas the 1938 Act permitted applications to take effect upon FDA inaction, the 1962 Amendments required FDA to "approve" a new-drug application. *Compare* FDCA § 505(c), 52 Stat. 1052, *with* 1962 Amendments § 104(b), 76 Stat. 784.

Even as the 1962 Amendments strengthened FDA's premarket-review authority, Congress made clear that

> [n]othing in the amendments made by this Act to the [FDCA] shall be construed as invalidating any provision of State law which would be valid in the absence of such amendments unless there is a direct and positive conflict between such amendments and such provision of State law.

1962 Amendments § 202, 76 Stat. 793.

State-law actions against drug manufacturers continued after the FDCA's enactment,[3] with courts rejecting arguments that the FDCA preempted such claims in the rare instances in which manufacturers raised that defense.[4]

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[3] *See, e.g., McEwen v. Ortho Pharm. Corp.*, 528 P.2d 522, 528 (Or. 1974) ("well settled" that drug maker "bears [a] duty of making timely and adequate warnings"); *see also Riegel*, 128 S. Ct. at 1017 & n.11 (Ginsburg, J., dissenting) (collecting cases); W. Page Keeton, *Prosser and Keeton on the Law of Torts* 688 (5th ed. 1984); Janet Fairchild, Annotation, *Liability of Manufacturer or Seller for Injury or Death Allegedly Caused by Failure To Warn Regarding the Danger in Use of Vaccine or Prescription Drug*, 94 A.L.R.3d 748 (1979).

[4] "Courts that have considered the question have overwhelmingly held that FDA approval of a new drug application does not preempt state tort suits." *Riegel*, 128 S. Ct. at 1018-19

3. To further the FDCA's purpose of ensuring accurate labeling bearing adequate warnings and instructions, *see* 21 U.S.C. §§ 331(a)-(c), 352(a), (f), FDA regulations have long permitted and encouraged drug manufacturers to update their labels to provide physicians with the most current information about the risks of their products, *see, e.g.*, 21 C.F.R. § 1.110(d) (1955) (authorizing "supplemental application" proposing changes in "labeling").

In 1965, FDA determined that certain important safety-based labeling changes should be implemented "at the earliest possible time." 30 Fed. Reg. 993, 993 (1965). Under FDA's amended rule, a manufacturer could augment the labeling with an "additional warning, contraindication, side-effect, and precaution information" when it submitted a supplemental application covering the change, without waiting for FDA's approval. *Id.* at 993-94 (promulgating 21 C.F.R. § 130.9(d)(1), (e) (1965)).

Consistent with Congress's purpose in the FDCA to protect consumers and the public health by prohibiting false and misleading labels, that regulation today provides that a drug manufacturer can make "[c]hanges [in] labeling" – *without* prior FDA approval – "[t]o add or strengthen a contraindication, warning, precaution, or adverse reaction" or "[t]o add or strengthen an instruction about dosage and administration that is intended to increase the safe use of the product." 21 C.F.R. § 314.70(c)(6)(iii)(A), (C). Under § 314.70(c)(6) – known as the "changes being effected" ("CBE") regulation – such labeling changes can be implemented when FDA receives the supplemental application reflecting the change

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(Ginsburg, J., dissenting) (collecting cases, *see id.* at 1017-19 & nn.11, 16).

and before FDA acts on that application. *See id.* § 314.70(c)(6).

Further, FDA has long required manufacturers to revise drug labeling "to include a warning as soon as there is reasonable evidence of an association of a serious hazard with a drug; a causal relationship need not have been proved." *Id.* § 201.80(e). As FDA explained when promulgating that regulation, "it is *essential* to the safe use of a drug for the physician to know *all* adverse reactions that are likely to occur with it"; "the act requires labeling to include warnings about both *potential* and verified hazards"; and the agency "believes that practicing physicians will welcome such information so that they can make their best informed medical judgments in the care of their patients." 44 Fed. Reg. 37,434, 37,443, 37,447 (1979) (emphases added).[5]

4. FDA has consistently encouraged manufacturers voluntarily to update their labeling because, at all times relevant to this case, it lacked the power to compel manufacturers to make specific labeling changes. As a senior FDA official testified to Congress in 2005, if FDA believed that a labeling change was necessary, it had to "negotiate" with the manufacturer because it did not have "the authority to tell a company, this is how your label has to look."[6] FDA's only recourse if a manufacturer refused to implement a labeling change was to withdraw its

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[5] *See also Werner v. Upjohn Co.*, 628 F.2d 848, 860 (4th Cir. 1980) ("FDA's regulations and policies encourage early unilateral action by the drug companies to improve their warnings").

[6] *FDA's Drug Approval Process: Up to the Challenge?: Hearing Before the S. Comm. on Health, Education, Labor, and Pensions*, 109th Cong. 23 (2005) (testimony of Sandra Kweder, M.D., Deputy Director, Office of New Drugs, FDA).

approval of the application under § 355(e)[7] or to initiate a misbranding action in federal court, with the misbranding question typically decided by a federal jury, *see* 21 U.S.C. §§ 331(a), 332, 333(a), 334(a)-(b).[8]

B. FDA Regulation of Phenergan

1. Phenergan is an anti-nausea drug prescribed and administered by physicians. JA38, 85, 390-91. It has a dangerous side effect: when exposed to arterial blood, Phenergan causes swift and irreversible gangrene. JA239 (Finding of Fact ("FOF") 1); JA57-59, 72-73.

In accordance with the labeling in effect at the time of Diana Levine's injury, Phenergan can be administered through an injection into the patient's muscle – intramuscular (IM) injection – or it can be introduced into the patient's vein. JA391.[9] Intravenous (IV) administration can be performed in two ways. In the first – "IV drip" – the medication is placed into a stream of saline flowing from a hanging IV bag into a vein in the patient's arm. JA49-51, 66-68, 239-40 (FOF 2). In the second – "IV push" – a medical practitioner injects the medication directly into the patient's vein using a syringe. JA46-47, 52-53, 88, 92.

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[7] FDA took that step only once, more than 30 years ago, in a case concerning a lethal side effect, not a labeling issue. *See* U.S. Gov't Accountability Office, *Drug Safety: Improvement Needed in FDA's Postmarket Decision-making and Oversight Process* 10 n.19 (Mar. 2006) ("GAO Drug Safety Report").

[8] The Food and Drug Administration Amendments Act of 2007 ("2007 Amendments") provided FDA with limited authority to order labeling changes after first negotiating with the manufacturer. *See* Pub. L. No. 110-85, § 901(a), 121 Stat. 823, 924-26 (codified at 21 U.S.C. § 355(*o*)(4)).

[9] A vein carries blood back to the heart; an artery carries blood from the heart to the capillaries of organs and tissue.

With IV push, Phenergan can be exposed to arterial blood inadvertently if the medical professional either punctures an artery directly or pierces the other side of the vein, causing the medication to "extravasate" – or exude from the vein – into the surrounding tissue and bathe an artery. JA67, 71, 240 (FOF 3). Even an experienced clinician exercising due care will, on occasion, inadvertently expose the medication to the patient's artery, rather than injecting it entirely into the vein. JA73, 75-76. Some patients have so-called "aberrant" arteries near the veins in their arms, thus heightening the risk of inadvertent arterial exposure from IV-push administration of Phenergan. JA54-55, 75-76, 78.

The IV-drip technique works differently. An IV drip is started with saline, which will not flow properly if the catheter is not entirely within the vein. Back-pressure from an artery will prevent the fluid from flowing into an artery; if the fluid is flowing into the tissue surrounding the vein, it fills the available space and has nowhere to go. Thus, at the outset of the IV-drip procedure, before any medication is introduced, the medical professional can readily determine whether the saline is flowing into the vein or escaping into an artery or surrounding tissue. JA49-51, 60, 66-68, 74-75, 108-09, 240 (FOF 4).

2. In 1967, Wyeth reported to FDA an adverse reaction evidently caused by exposure of Phenergan to blood in a patient's artery through a method of intravenous administration Wyeth did not identify to FDA and does not here assert to have been IV push (Br. 12). Although Phenergan's "direction circular" at that time warned against intra-arterial injection, a physician administering the drug intravenously nonetheless inadvertently caused the drug to enter

the patient's artery, causing "gangrene of the arm and subsequent amputation." JA268-69.

In 1973, Wyeth submitted a supplemental application for Phenergan that included revised labeling. JA270. FDA "recommend[ed]" a series of changes to Wyeth's proposed package insert. JA271. One was to change the "Warnings" section to note that the "intravenous use of" Phenergan "is not without hazard." *Id.* That suggestion duplicated the statement in the "Dosage and Administration" section that "proper intravenous administration of promethazine hydrochloride is well tolerated, but use of this route is not without some hazard." JA277.

In 1975, Wyeth submitted another supplemental application containing revised labeling for Phenergan. JA280. FDA again wrote Wyeth with revisions that "should" be made to the proposed label. *Id.* Most did not pertain to the risk of arterial exposure. JA280-86. FDA suggested that a warning, in capital letters, about arterial exposure be included in the "Cardiovascular Effects" section. JA283. FDA also recommended an addition to the Warnings section to clarify that medical practitioners cannot rely on the color of the blood drawn back into an intravenous setup to determine whether it is venous (dark red) or arterial (bright red) blood, because Phenergan discolors arterial blood. JA282. Consistent with FDA's lack of authority to require label changes for previously authorized drugs, *see supra* p. 8, Wyeth declined to implement many of FDA's recommendations. *Compare* JA281 (FDA recommending a warning to reduce dosages for elderly patients) *with* JA290 (noting that Wyeth "disagree[d]" with that recommendation).

In 1976, an FDA advisory committee met to discuss a number of topics, including revisions to the proposed Phenergan package insert that FDA had suggested and Wyeth had rejected. JA287-95.[10] Disagreeing with FDA, the committee "had no objections" to Wyeth's proposal to continue to contraindicate – that is, recommend against – arterial injection of Phenergan (FDA evidently had opposed the contraindication as unnecessary, because "arterial injection is not an acceptable means of administering drugs"). JA289. The committee also recommended warning practitioners to inject the drug "into a satisfactorily functioning intravenous set." JA294. Nothing in the advisory committee's minutes indicates that it considered (or was asked to consider) whether to include a specific warning about IV-push injection or to recommend against IV-push injection entirely.

In 1979, FDA promulgated a rule to standardize the formatting of prescription drug labeling. Although FDA required manufacturers to submit reformatted labeling for approval, it made clear that the rule did not supersede provisions allowing manufacturers to change labeling to add or strengthen a warning.[11] FDA also specified that it did not "inten[d]" "to influence the civil tort liability of the manufacturer," 44 Fed. Reg. at 37,437, and cited approvingly a state appellate decision upholding a plaintiff's verdict in a

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[10] FDA uses advisory committees of outside experts to advise it on a variety of issues. *See generally Food and Drug Law* 1573-88.

[11] *See* 44 Fed. Reg. at 37,438 ("Labeling revisions that may be placed into effect without FDA approval, such as the addition of a warning," would not require "the revision of the labeling to comply with these final regulations in advance of the scheduled revision date for the drug.").

failure-to-warn case, *see id.* at 37,447 (citing *McEwen v. Ortho Pharm. Corp.*, *supra*).

In 1981, Wyeth filed a supplemental application proposing revised Phenergan labeling to comply with the 1979 rule. JA297-306. In 1987, FDA recommended revisions to, among other things, the proposed warning on intra-arterial injection. JA311-15. Neither Wyeth's proposal nor FDA's recommended revisions restricted use of IV-push administration. *Compare* JA300-06 *with* JA310-19. In 1988, Wyeth submitted revised labeling incorporating FDA's requested revisions, along with additional changes of its own. *Compare* JA325-26, 328-30, 334-35, 339-41 *with* JA311-15.

In 1996, FDA requested from Wyeth the package insert then in use for Phenergan. JA347. In 1997, FDA informed Wyeth that its proposed labeling revisions were "approvable" subject to certain further revisions. JA355-56. Relevant here, FDA did not endorse its 1987 proposed revisions (JA311-15) to the warning on inadvertent intra-arterial injection. It stated – without further explanation – that Wyeth instead should "[r]etain verbiage in current label," meaning the version of the label Wyeth submitted at FDA's request in 1996. JA350, 359. The government here explains that statement as follows: "it appears that FDA viewed the change" Wyeth submitted in 1988 at FDA's request "as non-substantive and rejected it for formatting reasons." U.S. Br. 25. Subsequently, in 1998, Wyeth submitted revised labeling incorporating FDA's comments, along with further modifications of its own. JA366-80. Later that year, FDA completed its "review" of Wyeth's 1981 supplemental application. JA382.

As Wyeth and the government here do not dispute, the correspondence between Wyeth and FDA provides no indication that the agency considered (at Wyeth's request or on its own) whether Phenergan's labeling should bear a specific warning on or prohibition of IV-push injection.

C. Ms. Levine's Injury

On April 7, 2000, Diana Levine went to a clinic near Marshfield, Vermont to treat a migraine headache. She received an intramuscular injection of Demerol (for her headache), along with Phenergan (for nausea, which is associated with a migraine headache and is a common side effect of Demerol). JA38, 237-38; Pet. App. 2a. After Ms. Levine's migraine recurred later that day, she returned to the clinic, where she received a second Demerol-Phenergan combination. In accordance with the instructions in Phenergan's package insert, the physician's assistant administered this dose of Phenergan through an IV-push injection into Ms. Levine's right arm. JA52-53, 88, 92, 104-06, 109-10, 191, 199, 210; Pet. App. 2a.

During the IV-push injection, the Phenergan penetrated one of Ms. Levine's arteries. JA240 (FOF 3); JA58. In the ensuing weeks, the tissue in her right forearm died and she experienced extreme pain. JA55-57, 127, 133-35, 154-55, 162-63, 165-68, 178-79; JA166 (expert testimony that the pain was "a ten" on a "[p]ain scale[]" of "one to ten"). Her fingers slowly turned black as they lost all blood circulation.[12]

Doctors initially amputated Ms. Levine's hand. JA163. After several days, during which the gangrene

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[12] *See* JA386-89 (before-and-after-injury photographs of Ms. Levine's arm).

spread down her forearm and Ms. Levine continued to experience excruciating pain, she underwent a second operation to amputate what was left of her forearm below her elbow. JA163-64. After her amputations, Ms. Levine has continued to experience physical and "phantom pain" in her right arm and tendonitis from over-using her left arm, while enduring emotional trauma and depression. JA156-57, 159-62, 169-72.

Before her injury, Ms. Levine was a professional musician who developed musical programs to perform with children. JA117-26, 130-32, 136-37, 386. She also performed live concerts and recorded her music for sale. JA118-19, 122-23, 132. After her arm was amputated, Ms. Levine could no longer play her guitar – her profession and lifelong passion. JA120. She struggles to perform daily tasks and household chores, and can no longer participate in outdoor activities she once enjoyed. JA123-24, 128-29, 137-54, 157-58, 168-69. She lost her livelihood and incurred hundreds of thousands of dollars in medical bills. JA173-76.

D. Proceedings Below

1. In Vermont Superior Court, Ms. Levine asserted state-law negligence and products-liability claims premised on Wyeth's failure to provide proper warnings and instructions regarding the foreseeable risks of IV-push injection of Phenergan. JA227-32. The amended complaint alleged that Phenergan was defective because, among other things, the company failed to instruct clinicians to administer the drug intravenously using the IV-drip technique. JA14 (¶ 5). Ms. Levine sought only damages, not an injunction requiring any labeling change. JA17.

The trial evidence, which the Court views in the light most favorable to Ms. Levine's verdict,[13] demonstrated that inadvertent arterial exposure – causing gangrene requiring amputation – can result from IV-push administration, even when performed by an experienced clinician. JA73, 75-76. Administering Phenergan using the IV-drip technique, by contrast, "almost precludes" inadvertent arterial contact. JA67; *see* JA49-51, 60, 66-68, 74-75, 108-09, JA240 (FOF 4). Further, the only benefit of IV-push administration, as compared to IV drip, is marginally faster relief from nausea. JA104, 106. Experts testified at trial that any such benefit would never justify a significantly increased risk of gangrene and that, if Phenergan is used intravenously, it should be injected only through a hanging IV bag and Wyeth's package insert should have precluded IV-push administration. JA59, 77-80, 96, 108-09; *see also* JA112 ("It's nausea. . . . [T]his isn't a heart attack, this is somebody who's sick to their stomach.").

A Wyeth expert testified that he could "conceive of" a circumstance in which IV-push injection of Phenergan might "theoretically" be medically appropriate – namely, if the patient had "been vomiting to the point of severe hypobulimia, fluid depletion, veins are very tough to get into." JA195. That expert also acknowledged, however, that he would hesitate to use IV-push injection in non-life-threatening situations and that he would have written the label to instruct that Phenergan be administered intravenously only through the IV-drip method. JA192-94. Another Wyeth expert, who neither treated migraines nor prescribed anti-nausea medications,

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[13] *E.g.*, *Brooke Group Ltd. v. Brown & Williamson Tobacco Corp.*, 509 U.S. 209, 213 (1993).

testified that the benefits of intravenous administration of Phenergan outweighed its risks in some circumstances, but he did not offer that opinion with respect to *IV-push* injection. JA200-01, 207-10.[14] (Wyeth offered no evidence it ever submitted or FDA considered analyses of such facts in making any labeling judgments concerning Phenergan.)

Wyeth also contended that the physician's assistant who administered the IV-push injection of Phenergan, not Wyeth, bore sole responsibility for Ms. Levine's injury (an argument Wyeth reiterates here, Br. 19-20 & n.10). Specifically, Wyeth alleged that the physician's assistant negligently administered the drug by continuing the injection after Ms. Levine cried out in pain and by exceeding the recommended dosage.

Ms. Levine's evidence rebutted Wyeth's attempt to blame the physician's assistant. The physician's assistant testified that, although Ms. Levine said that the medicine "burned," she completed the injection because the injection site looked fine, the Phenergan was flowing normally, and Ms. Levine's complaints of discomfort were not unusual. JA111, 116; *see also* JA185 (testimony of Ms. Levine that she did not scream). Testimony also established that stopping the injection when Ms. Levine expressed discomfort would not have prevented her injury. JA57-59, 239 (FOF 1); *see also* JA72-73, 80. In addition, an expert testified that, although the label stated that the "usual" dose for nausea was 12.5 to 25 milligrams (JA391), a 50-milligram dose was appropriate under the circumstances. JA41; *see also* JA105.

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[14] *Compare* JA84 (testimony of Dr. Harold Green that he could not recall a case in which a patient needed immediate relief of nausea).

2. The trial judge instructed the jury that "the disputed issue is whether the warning and instructions provided by Wyeth were adequate concerning the risks of injection of [Phenergan]. The warning must reasonably advise of the risks and provide adequate instructions to the medical professionals for its safe use." JA231-32. The judge also instructed the jury on Wyeth's regulatory-compliance defense, explaining that the jury could "consider evidence of compliance by Wyeth with FDA requirements in obtaining approval for the Phenergan warning." JA227. The instructions explained that FDA's CBE regulation permits drug makers to change their labels without prior FDA approval to add or strengthen a warning. JA228. Wyeth did not object to those instructions, although it objected to others. JA223.

In the summation, Ms. Levine's counsel told the jury, "You will make the decision" whether Wyeth adequately warned against arterial exposure during IV-push injection of Phenergan. JA211. That statement accurately reflected the trial record: because Wyeth introduced no evidence that FDA ever considered (or was asked to consider) the relative benefit of relieving nausea a few minutes faster versus the risk of losing a limb – or the associated risks of IV push versus other methods of administration – the decision whether Wyeth adequately warned of IV-push injection risks was for the properly instructed jury to make.

In its verdict, the jury specifically rejected Wyeth's contention that unforeseeable negligence of the physician's assistant, rather than Wyeth's failure to warn, caused Ms. Levine's injury. JA233-35; *see also* JA230-32, 252 (intervening-cause issue "raises factual issues which were argued to the jury and

resolved in plaintiff's favor at trial"). The jury awarded damages to compensate Ms. Levine's economic and non-economic losses – including past and future medical expenses and the loss of her ability to earn a living (evidence Wyeth did not dispute, *see* JA259). The trial judge found Ms. Levine's injuries to be "tragic," "horrific," and "as bad an injury case as any court is likely to see." JA258-59.

The trial court denied Wyeth's post-judgment motion asserting preemption. The court recognized that Wyeth could comply with both Vermont law and federal law, because FDA's CBE regulation permitted Wyeth to change its labeling to prohibit IV-push administration or strengthen the warnings about IV push without prior FDA approval. JA250-51. (Wyeth never asserted at trial that the CBE regulation applied only to labeling changes based on "new" information.)

The court also held that its judgment posed no obstacle to Congress's purposes in the FDCA. It found "no evidence in this record that either the FDA or the manufacturer gave more than passing attention" to whether the label should preclude IV-push injection. JA249. It further explained that this case posed little or no risk that an unwarranted warning might deter beneficial uses of a drug, because Ms. Levine's claim related "only to the method of administration, not to the decision to use Phenergan." JA250. That made this case "different from cases involving proposed warnings of remote side effects [that] might dissuade physicians from using the drug to the detriment of the patient population." *Id.*

3. The Vermont Supreme Court affirmed, concluding that Wyeth had shown no "actual[] conflict[]" between the trial court's judgment and federal law.

Pet. App. 8a (internal quotation marks omitted). The court explained that compliance with both federal law and a state-law duty to warn is possible, because FDA's regulations "allow[], and arguably encourage[], manufacturers to add and strengthen warnings that, despite FDA approval, are insufficient to protect consumers." *Id.* at 11a (citing 21 C.F.R. § 314.70(c)); *see id.* at 17a. "State tort claims," the court explained, "simply give these manufacturers a concrete incentive to take this action as quickly as possible." *Id.* at 11a.

The court further found that the "record lacks any evidence" that FDA would have "prohibited the use of a stronger warning with respect to IV-push administration of Phenergan." *Id.* at 16a. As the court reasoned, "[n]either the letters [Wyeth and FDA exchanged] nor any other evidence presented to the jury indicated that the FDA wished to preserve the use of IV push as a method of administering Phenergan." *Id.* at 17a; *see also id.* at 18a n.2.

The court also rejected Wyeth's argument that the trial court's judgment posed an obstacle to Congress's objectives in the FDCA. *See id.* at 15a, 19a. It explained that "there is no conflict between federal objectives and Vermont common law," because "FDA and the state share the purpose of encouraging pharmaceutical companies to alter their drug labels when they are inadequate to protect consumers." *Id.* Chief Justice Reiber dissented. *Id.* at 35a-48a.

SUMMARY OF ARGUMENT

I. Because this Court presumes that Congress "does not cavalierly pre-empt state-law causes of action," *Medtronic, Inc. v. Lohr*, 518 U.S. 470, 485 (1996), Wyeth must demonstrate clear congressional intent to preempt Ms. Levine's claims. Wyeth cannot do so.

When Congress enacted the FDCA, a well-established body of state-law remedies existed for patients injured by defective drugs – including drugs lacking adequate warnings and instructions. Against that backdrop, Congress in the FDCA neither provided a federal right of action nor expressed any intent to preempt state-law actions. In the 70 years since the FDCA was enacted, courts have continued to adjudicate state-law failure-to-warn claims, and Congress has amended the statute on numerous occasions. Although it chose expressly to preempt claims against device manufacturers, it never passed a similar provision for drug makers. Moreover, Congress took other actions that would have been meaningless if the FDCA already had immunized drug manufacturers from lawsuits. That statutory history reinforces that Congress never intended the FDCA to preempt state-law claims.

II. Ms. Levine's state-law claim is not impliedly preempted on the ground that it is "impossible" to comply with both state and federal law.

A. The FDCA does not preclude drug manufacturers from adding or strengthening warnings or instructions regarding their products. Wyeth could have added a stronger warning against IV-push injection at the inception of its FDA approval process or after the drug was approved, through a labeling change.

Without any textual support for its conflict preemption argument, Wyeth erroneously contends that it would be liable for misbranding or distributing an unauthorized new drug if it complied with the state-law duty to warn of IV-push risks. A drug is not misbranded if it contains true and accurate information about the risks associated with a particular method of administration. There is no credible claim that a court would have rejected a stronger warning or instruction regarding IV-push injection. And Wyeth's criticisms of juries are misdirected, because federal juries decide allegations of misbranding. Nor would adding or strengthening a warning or instruction regarding IV push have transformed Phenergan into an unauthorized new drug. Its use would have been for the same purpose; the only changes would warn of significantly greater risks from IV-push injection versus other forms of administration.

B. Federal law did not prohibit Wyeth from providing a stronger warning or instruction regarding IV-push injection. Wyeth could have strengthened the Phenergan labeling initially or changed it after FDA approval consistent with FDA regulations. FDA seeks all relevant risk information prior to a drug's approval, and the CBE regulation, 21 C.F.R. § 314.70(c)(6), permits manufacturers to change drug labeling to add or strengthen a warning or instruction. Wyeth and the government argue that the CBE regulation does not apply here because CBE supplements must be based on newly discovered risk information. But the regulation's text contains no such limitation. And the government cannot claim deference for its a-textual interpretation of the CBE regulation, both because the regulation's language contains no ambiguity and because courts do not

defer to agency efforts to re-write regulations through purported interpretation. In any event, FDA has interpreted its CBE rule to permit labeling changes based on re-analysis of existing information, which Wyeth should have done with Phenergan.

C. Because Ms. Levine did not seek (and was not awarded) injunctive relief, Wyeth could comply with the judgment below by paying the damages awarded to Ms. Levine for her injuries. The incidental regulatory consequences of tort judgments do not create impossibility conflicts with the federal regime, which still permits Wyeth to sell its drug and enables the manufacturer to conduct its own cost-benefit analysis of compliance with state-law duties of due care in particular factual circumstances.

III. The Vermont judgment poses no obstacle to Congress's purposes in the FDCA. On the contrary, state and federal law impose complementary duties. Both Vermont law and the FDCA require drug manufacturers to provide adequate warnings and instructions regarding their products. As this Court's cases recognize, state-law claims promote federal labeling rules by encouraging manufacturers to discover and to disseminate the most current information about the risks of their products. Vermont law also follows the general rule permitting manufacturers to present evidence of compliance with the FDCA and FDA regulations in defending failure-to-warn suits. Through the regulatory-compliance defense, state law supports the federal regulatory scheme by providing a compensatory mechanism federal law lacks and an additional incentive for manufacturers to use due care in providing appropriate warnings.

Wyeth argues, however, that the Vermont judgment poses an obstacle to the federal regime because

FDA balanced the relevant risks and benefits and determined that the Phenergan labeling regarding IV-push injection was appropriate. But, as the Vermont courts found, the record contains no evidence that FDA ever weighed the risks and benefits of *IV-push* administration of Phenergan or made a judgment that some benefit of IV-push injection in treating nausea justified its increased risks of gangrene requiring amputation. Thus, the Vermont courts' determination that Phenergan's labeling inadequately warned of the risks of IV-push injection did not contradict any deliberate federal judgment.

The government asserts that a state-law claim is preempted so long as the agency knew the relevant risk – broadly defined – when it approved the labeling. That new and overly broad position would eliminate state-law remedies without requiring proof that FDA made a judgment conflicting with the state-law duty in question. Here, the issue is not knowledge that arterial exposure to Phenergan causes gangrene; rather, it is knowledge that the IV-push administration method poses significantly higher risks of that adverse effect without any countervailing benefit. Because FDA took no action on IV push from any Wyeth submission or on its own, conflict preemption is inapplicable.

Finally, the Court should give no weight to the government's view that the FDCA preempts state-law claims. As the government concedes, any weight given to its views would be determined in accordance with *Skidmore v. Swift & Co.*, 323 U.S. 134 (1944). But even *Skidmore* consideration must take into account the inconsistency and current unpersuasiveness of FDA's positions. FDA's assertion now that the FDCA generally preempts state-law failure-to-

warn claims represents a policy reversal – not a law-based change – when for many decades FDA viewed common-law claims as complementary to its regulatory efforts.

ARGUMENT

Preemption "fundamentally is a question of congressional intent." *English v. General Elec. Co.*, 496 U.S. 72, 78-79 (1990); *see Puerto Rico Dep't of Consumer Affairs v. Isla Petroleum Corp.*, 485 U.S. 495, 503 (1988) ("There is no federal pre-emption *in vacuo*, without a constitutional text or a federal statute to assert it."). Accordingly, the "purpose of Congress is the ultimate touchstone of pre-emption analysis." *Cipollone v. Liggett Group, Inc.*, 505 U.S. 504, 516 (1992) (internal quotation marks omitted).

Because Congress included no express preemption provision in the FDCA and because Wyeth concedes (at 52-53) that the FDCA does not preempt the field of drug labeling,[15] Wyeth can prevail only by demonstrating that Vermont law "actually conflicts" with federal law. *English*, 496 U.S. at 79. An "actual conflict" exists when "it is impossible for a private party to comply with both state and federal requirements, or where state law stands as an obstacle to the accomplishment and execution of the full purposes and objectives of Congress." *Sprietsma v. Mercury Marine*, 537 U.S. 51, 64 (2002) (citations and internal quotation marks omitted). Conflict-

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[15] *See also* JA261-62 (Wyeth counsel oral argument, Vermont Supreme Court) ("Wyeth is not contending for a field preemption, for the ouster of Vermont law, tort law, not at issue here. . . . [N]or are we arguing that the mere compliance with the federal labeling requirements in and of itself creates a conflict preemption[.]"); Pet. App. 8a (noting Wyeth's "conce[ssion]" on this point).

preemption analysis is not, however, a "'freewheeling judicial inquiry into whether a state statute is in tension with federal objectives,' but an inquiry into whether the ordinary meanings of state and federal law conflict." *Bates v. Dow AgroSciences LLC*, 544 U.S. 431, 459 (2005) (Thomas, J., concurring in the judgment in part and dissenting in part) (quoting *Gade v. National Solid Wastes Mgmt. Ass'n*, 505 U.S. 88, 111 (1992) (Kennedy, J., concurring in part and concurring in the judgment)) (citation omitted). Ms. Levine's state-law claims readily survive implied conflict preemption.

I. CONGRESS'S LONG ACCEPTANCE OF STATE-LAW FAILURE-TO-WARN CLAIMS AGAINST DRUG MANUFACTURERS DECISIVELY UNDERMINES WYETH'S IMPLIED PREEMPTION ARGUMENT

In the FDCA, Congress emphasized consumer safety as a paramount goal. To that end, it established that:

- Introduction of any "misbranded" drug would be "prohibited," 21 U.S.C. § 331(a);
- A drug label would be "misbranded" if "false or misleading in any particular," *id.* § 352(a); and
- Such labeling would be misbranded if it lacked "adequate warnings . . . against unsafe dosage or methods or duration of administration or application," *id.* § 352(f).

Under Vermont law, as in states generally, a failure-to-warn claim imposes on drug companies "a duty to take reasonable steps to notify users of the product – in this case the medical community – of the risks and dangers of the product and to provide adequate instructions about how to use the product

safely." JA228 (jury instructions). Such claims directly parallel federal misbranding requirements. *Cf.* 21 U.S.C. § 352(f).

The long history of state-law failure-to-warn claims against pharmaceutical manufacturers, *see supra* notes 1 & 3, and Congress's consistent acceptance of such actions, undermine Wyeth's assertion that state-law claims conflict with federal law. In evaluating preemption of longstanding state-law remedies, this Court's decisions require a "clear[]" indication of Congress's intent. *Bates*, 544 U.S. at 449.[16]

A. In The FDCA And Its Amendments, Congress Expressed No Intent To Preempt State-Law Failure-To-Warn Claims Against Drug Manufacturers

Congress has never enacted a prescription-drug preemption provision, despite numerous opportunities to do so. Its enactment of a preemption provision for medical devices, but not drugs, strongly signals its intent to preserve state-law remedies against pharmaceutical manufacturers. *See Riegel*, 128 S. Ct. at 1009 ("Congress could have applied the pre-emption clause" in the Medical Device Amendments of 1976 "to the entire FDCA," but it "instead wrote a pre-emption clause that applies only to medical devices"); *see also id.* at 1017 (Ginsburg, J., dissenting) ("Nothing in the FDCA's text or legislative history suggested that FDA preclearance would immunize drug manufacturers from common-law tort suits."). In fact, Congress demonstrated its intent to preserve state-law claims by declining to include in the 1938

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[16] *See Lohr*, 518 U.S. at 485; *Silkwood v. Kerr-McGee Corp.*, 464 U.S. 238, 251 (1984); *see also Bonito Boats, Inc. v. Thunder Craft Boats, Inc.*, 489 U.S. 141, 166-67 (1989).

Act a federal private right of action against drug makers based on testimony that state-law remedies were sufficient. *See supra* p. 4 & n.2.

Against that backdrop of existing common-law claims and precedent rejecting assertions of preemption, subsequent congressional actions bolster the inference that Congress has not intended to preempt state-law damages suits against drug manufacturers.[17] In 1997, for example, Congress added provisions pre-empting some state statutory and regulatory requirements for over-the-counter drugs. *See* Food and Drug Administration Modernization Act of 1997 ("1997 Act"), Pub. L. No. 105-115, § 412(a), 111 Stat. 2296, 2373-75 (codified at 21 U.S.C. § 379r(a)-(d)). The new section expressly disclaimed any effect on "the liability of any person under the product liability law of any State." *Id.* at 2375 (codified at 21 U.S.C. § 379r(e)).[18] And, in 1995, the House passed a bill to eliminate punitive, but not compensatory, damages recoverable against drug manufacturers where FDA approved the drug's "labeling." H.R. 956, 104th Cong. § 201(f) (1995) (as passed by House, Mar. 10,

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[17] *Cf. FDA v. Brown & Williamson Tobacco Corp.*, 529 U.S. 120, 143-59 (2000); *Albemarle Paper Co. v. Moody*, 422 U.S. 405, 414 n.8 (1975); *cf. also Branch v. Smith*, 538 U.S. 254, 280-81 (2003) (plurality opinion).

[18] *See* S. Rep. No. 105-43, at 66 (1997) ("[T]he legislation explicitly provides that it shall not be construed to modify or otherwise affect the traditional product liability law of any State. Tort liability rules and requirements would remain unchanged and unaffected."); *see also* 1997 Act § 131, 111 Stat. 2332 (requiring manufacturers of life-saving drugs to provide FDA six months' notice before discontinuing manufacture of such a drug and reducing period if "a *liability problem* may exist for the manufacturer if the manufacturing is continued") (emphasis added) (codified at 21 U.S.C. § 356c(b)(3)).

1995). That bill also would have limited non-economic damages to $250,000 in "any health care liability action," defined to include actions against "the manufacturer" of "a medical product." *Id.* § 203(a), (c)(3).[19]

The 1995 and 1997 bills would have been largely meaningless if state tort suits against drug manufacturers – the vast majority of which were failure-to-warn claims[20] – had already been preempted.

B. The Statutory History Supports A Presumption Against Preemption

The absence of any FDCA preemption clause for prescription drugs, combined with subsequent congressional actions that make sense only against the backdrop of state-law liability, confirms the importance of applying this Court's longstanding presumption against preemption. The Court has "never assumed lightly that Congress has derogated state regulation, but instead ha[s] addressed claims of pre-emption with the starting presumption that Congress does not intend to supplant state law." *New York State Conference of Blue Cross & Blue Shield Plans v. Travelers Ins. Co.*, 514 U.S. 645, 654-55 (1995). That presumption against preemption "provides assurance that the federal-state balance will not be disturbed unintentionally by Congress or unnecessarily by the courts." *Jones v. Rath Packing Co.*, 430 U.S. 519, 525 (1977) (citation and internal

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[19] A subsequent version of the legislation passed both houses of Congress, but was vetoed. *See* 32 Weekly Comp. Pres. Doc. 780 (May 2, 1996).

[20] *See Restatement (Third) of Torts: Products Liability* § 6 cmt. d (1998) ("[f]ailure to instruct or warn is the major basis of liability for manufacturers of prescription drugs").

quotation marks omitted); *see also Lohr*, 518 U.S. at 485.[21] Wyeth therefore must show a conflict between the FDCA and the Vermont judgment "that is strong enough to overcome the presumption that state and local regulation of health and safety matters can constitutionally coexist with federal regulation." *Hillsborough County v. Automated Med. Labs., Inc.*, 471 U.S. 707, 716 (1985).[22]

Wyeth cannot meet that burden. The broad theory of preemption advanced by Wyeth and its *amici* posits that FDA's approval of a drug's labeling constitutes both a "floor" and a "ceiling" and preempts any state law that might affect the labeling in any way. Wyeth Br. 45; U.S. Br. 19. Congress's history of acquiescence in, and this Court's precedents recognizing the presumptive validity of, traditional

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[21] *See* Brief for the United States as Amicus Curiae Supporting Petitioner at 17, *Buckman Co. v. Plaintiffs' Legal Comm.*, 531 U.S. 341 (2001) (No. 98-1768) ("claims of . . . negligent failure to warn . . . implicate[] core areas of traditional state concern").

[22] Wyeth asserts (at 51 n.23) that the presumption against preemption does not apply here because federal statutes have regulated the drug industry for a number of years. But, in *Bates* and *Lohr*, federal regulation had existed since 1910 and 1938, respectively, *see Bates*, 544 U.S. at 437; *Lohr*, 518 U.S. at 475, and this Court nonetheless applied its presumption against preemption. Wyeth cites cases involving areas of traditional, longstanding, and nearly exclusive *federal* concern. *See United States v. Locke*, 529 U.S. 89, 108 (2000) ("national and international maritime commerce," in which, "from the earliest days of the Republic," "Congress has legislated"); *Buckman Co. v. Plaintiffs' Legal Comm.*, 531 U.S. 341, 347 (2001) ("[p]olicing fraud against federal agencies"). The presumption against preemption applies with special force where, as here, preemption is asserted for federal regulatory action to override state law in the absence of a federal statute expressing an intent to displace state law, and federal law does not provide any private right of action.

state-law remedies against drug manufacturers rebut that claim. Nothing in the FDCA's history suggests that Congress either viewed state-law claims intended to promote public safety and compensate injured patients as conflicting with the federal scheme or intended to allow FDA to immunize drug manufacturers from such claims.

II. IT IS NOT IMPOSSIBLE FOR WYETH TO COMPLY WITH FEDERAL LAW AND THE STATE-COURT JUDGMENT

This Court has said on many occasions that federal law preempts state law when "compliance with both federal and state regulations is a *physical impossibility*." *Florida Lime & Avocado Growers, Inc. v. Paul*, 373 U.S. 132, 142-43 (1963) (emphasis added). But that rarely met test does not require preemption so long as compliance with federal and state law is "theoretically possible." *California Fed. Sav. & Loan Ass'n v. Guerra*, 479 U.S. 272, 291 (1987) (internal quotation marks omitted).

Wyeth can comply with both a damages judgment in a failure-to-warn case and the FDCA, which does not expressly preempt state law. Vermont law duties are consistent with federal law, because nothing in the statute or FDA's regulations prohibits manufacturers from proposing stronger warnings or later strengthening them to promote the drug's safe use. Independently, Wyeth could have complied with the Vermont judgment without changing its label.

A. The FDCA Did Not Compel The Specific Warning Found Inadequate In This Case And Permits Drug Manufacturers To Strengthen Warnings

Federal law did not compel the particular warning Wyeth used. Either in the initial proposed labeling for Phenergan before FDA approved the drug or after FDA approval, Wyeth could have warned of the special hazards of IV-push injection consistent with the FDCA. Congress recognized that pharmaceutical manufacturers have access to far greater information than FDA, which is why drug makers have always had the responsibility for drafting the warnings in prescription drug labeling. Insofar as Wyeth contends that, once FDA approves drug labeling, the FDCA bars a manufacturer from changing that labeling, that broad assertion finds no support in the FDCA's text. Wyeth's argument also cannot be squared with a prominent FDA regulation, 21 C.F.R. § 314.70(c)(6), that expressly permits such changes to strengthen inadequate warnings. Although the parties dispute the reach of that regulation, *see infra* Part II.B.3, under some circumstances the regulation unquestionably allows a manufacturer to implement stronger warnings while seeking FDA approval. If the FDCA barred *all* unapproved labeling revisions, that regulation necessarily would be facially invalid, a conclusion neither Wyeth nor FDA supports. Indeed, the government acknowledges (at 3 n.1) that the FDCA does not preclude a manufacturer from changing the labeling submitted with an approved new-drug application.

Wyeth seeks to evade the absence of textual support for its argument by asserting (at 30-31) that, if it had changed the Phenergan package insert to

comply with Vermont's duty of due care, it would have violated the FDCA's prohibitions on "misbranding" and "unauthorized distribution." Neither contention has merit.

1. Changing the Phenergan labeling to add a warning about IV push would not have caused the drug to be misbranded under the FDCA, 21 U.S.C. § 331(a). Indeed, the state-law duty runs parallel to the federal misbranding standard. A drug is "misbranded" if, among other things, its labeling is "false or misleading" or fails to include "such adequate warnings . . . where its use may be dangerous to health, or against unsafe dosage or methods or duration of administration or application." *Id.* § 352(a), (f). The Act nowhere provides that a drug is misbranded simply because the manufacturer changes the labeling submitted to FDA during the pre-market review process under § 355. *See id.* § 352. And Wyeth's supposition that federal law would prohibit a drug maker from enhancing warnings when one method of administering the drug significantly increases the risk of traumatic injury is directly contradicted by § 352(f)'s plain text, in which Congress sought to protect public health by insisting on adequate warnings.

Moreover, the congressional misbranding scheme does not confer exclusive authority on FDA to make misbranding determinations. Rather, Congress explicitly envisioned that, in any misbranding enforcement action, the question whether a drug's labeling is "false or misleading" or fails to contain adequate warnings would be decided in federal court – typically with a *jury* resolving FDA's allegations of misbranding. *See id.* §§ 332, 333(a), 334(a)-(b); *see also Lewis v. United States*, 518 U.S. 322, 326 (1996). "[L]ay juries," therefore, "are in no sense anathema to" the

FDCA's scheme. *Bates*, 544 U.S. at 452 (rejecting pro-preemption argument based on mistrust of juries because, in prosecutions under federal pesticide law, "juries necessarily pass on allegations of misbranding").

Wyeth's argument thus boils down to a dubious hypothetical: if Wyeth had changed its labeling after FDA approval, FDA would have decided to bring a misbranding action against it, and a federal jury or judge would have found that a stronger warning or instruction regarding IV-push injection would have rendered the labeling "false or misleading" or otherwise inadequate under the statute. That "hypothetical" possibility "is insufficient to warrant the pre-emption." *Rice v. Norman Williams Co.*, 458 U.S. 654, 659 (1982); *see also English*, 496 U.S. at 90 ("The teaching of this Court's decisions . . . enjoin[s] seeking out conflicts between state and federal regulation where none clearly exists.") (internal quotation marks omitted, alterations in original). The notion that an increased warning about IV-push injection would cause Wyeth to be liable for misbranding is particularly farfetched considering the overwhelming record evidence that IV-push injection's risks far outweigh any supposed benefits.

Notably, the government does not even suggest (as it has in other failure-to-warn cases) that it would have instituted a misbranding prosecution if Wyeth had used a stronger IV-push warning. *Compare, e.g.*, Brief of the United States as Amicus Curiae in Support of Defendants-Appellees at 16, *Colacicco v. Apotex, Inc.*, 521 F.3d 253 (3d Cir. 2008) (No. 06-3107) (asserting that the warning the plaintiff sought would have misbranded the drug), *with* U.S. Br. 21. Nor has Wyeth or the government identified any

case in which the government pursued a misbranding action against a drug manufacturer for strengthening its labeling. Indeed, in 2008, FDA responded to a congressional inquiry by identifying *no* instances in which it had concluded that a stronger warning implemented through a CBE supplement would harm public health.[23]

2. Wyeth also incorrectly asserts (at 30) – without explanation or authority – that a change in Phenergan's labeling regarding IV-push injection, without more, would have subjected it to liability for "unauthorized distribution." (The government does not make that argument.) The FDCA prohibits the introduction into interstate commerce of "any new drug" unless "an approval of an application" under § 355 "is effective with respect to such drug." 21 U.S.C. § 355(a); *see also id.* § 331(d). Wyeth's "unauthorized distribution" argument assumes that any change in an approved drug's labeling renders it a "new drug" "with respect to" which "an approval of an application" under § 355 is not "effective." *Id.* § 355(a).

That assumption is unfounded. With exceptions not relevant here, the FDCA defines a "new drug" as a drug that is "not generally recognized" by experts "as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof." *Id.* § 321(p)(1). Under that definition,

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[23] *See* Letter from Stephen Mason, FDA, to Hon. Henry Waxman 3-4 (Mar. 7, 2008). That letter identified only four instances since 2004 in which FDA did not approve a CBE supplement seeking to add or strengthen a contraindication, warning, precaution, or adverse reaction. In three of those cases, FDA determined that a *stronger* warning was necessary; in the other case, the warning was approved after the manufacturer submitted additional data.

if a manufacturer were to add a "condition[]" for "use" to a drug's label, the drug conceivably would be different from the "new drug" covered by the approved application. Had Wyeth changed its package insert to market Phenergan as a cancer-treating drug, that labeling might have made Phenergan a "new drug" within the meaning of § 321(p)(1). But adding or strengthening the warning on arterial exposure to address the greater risks with IV-push injection versus IV drip, or to preclude IV-push injection altogether, would not have added any new condition for use.[24] Therefore, Wyeth would have faced no liability under § 355(a) if its warning complied with Vermont's legal duties.

B. FDA Regulations Encourage And Permit Changes In Labeling To Increase Safety

Wyeth erroneously claims that any labeling different from the package insert used in Ms. Levine's case would have violated FDA regulations. That assertion is incorrect in three respects.

1. It is not impossible to comply with a state-law failure-to-warn judgment and FDA's initial approval of a drug. FDA approval signifies federal acceptance of a drug for marketing based on risk information presented to FDA. A state-law negligence judgment does not negate federal approval of a drug. A manufacturer may still market the drug, although the

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[24] Under an FDA regulation, the *addition* to the label of "a dosage, or method or duration of administration or application, or other condition of use," "may" cause the agency to conclude that it is a "new drug" under the FDCA. 21 C.F.R. § 310.3(h)(5). But that regulation does not support the conclusion that the agency would consider the *removal* of a method of administration – or the addition of a stronger warning regarding that method – to render a drug "new."

incident giving rise to the plaintiff's injury may trigger federal regulatory obligations for adverse-event reporting and the updating of warnings. *See* 21 C.F.R. §§ 201.80(e), 314.80. A manufacturer can readily comply with those additional reporting requirements while also adhering to state-law duties of due care in providing adequate warnings.

2. Wyeth also could have complied with Vermont state-law standards and federal regulations by submitting a supplemental application for FDA approval to strengthen its label to address IV-push injection risks. *See* 21 C.F.R. § 314.70(c)(6). Neither Vermont law nor the other hundreds of damages judgments against drug manufacturers over the years required labeling changes *without* seeking FDA's approval. And it is not impossible now for Wyeth to comply with the judgment below while seeking FDA approval of a labeling change. Because FDA cannot stop a manufacturer from withdrawing a drug from the market, it is illogical to suppose that FDA can prohibit a drug manufacturer from taking the lesser step of withdrawing a method of administering that drug. In any event, Wyeth cannot prevail on a conflict preemption claim when it never sought (or was denied) FDA approval for an enhanced warning on IV-push injection.

3. a. In the circumstances here, Wyeth can comply with the state-law duty by changing its label even *without* FDA's prior approval, as the very regulation Wyeth claims as conflicting provided. The CBE regulation provides, in pertinent part:

> The agency may designate a category of changes for the purpose of providing that, in the case of a change in such category, the holder of an approved application may commence distribu-

tion of the drug product involved upon receipt by the agency of a supplement for the change. These changes include, but are not limited to:

. . .

(iii) Changes in the labeling . . . to accomplish any of the following:

(A) To add or strengthen a contraindication, warning, precaution, or adverse reaction;

. . .

(C) To add or strengthen an instruction about dosage and administration that is intended to increase the safe use of the drug product . . . .

21 C.F.R. § 314.70(c)(6)(iii)(A), (C).

In 2007, Congress explicitly approved of FDA's CBE regulation, which permitted labeling changes to be made pending applications for approval. Section 901(a) of the 2007 Amendments, which gave FDA limited authority to order labeling changes after first negotiating with the manufacturer, *see supra* note 8, contains a "rule of construction" stating that the amendment "shall not be construed to affect the responsibility of" the drug company "to maintain its label in accordance with existing requirements, including subpart B of Part 201 and sections *314.70* and 601.12 of title 21, Code of Federal Regulations (or any successor regulations)." 121 Stat. 925-26 (emphasis added) (codified at 21 U.S.C. § 355(*o*)(4)(I)). That provision reflects Congress's intent that manufacturers possess the authority (and responsibility) to modify their labeling as needed to promote safety. And it undermines Wyeth's claim (at 35) that

manufacturer-initiated labeling changes are somehow contrary to the FDCA scheme.[25]

b. Wyeth and the government wrongly contend that the CBE regulation would not have permitted Wyeth to change its label to comply with a state-law duty to warn of IV-push injection risks or to instruct against IV-push injection. They assert that the CBE regulation applies only when the information motivating the labeling change is "new" or was not "previously available to the agency." U.S. Br. 24. That new argument – which Wyeth never raised at trial and the government apparently discovered only recently, after Ms. Levine's injury – cannot be squared with the regulation's unambiguous text, which contains no "new information" limitation.

The government claims the Court should defer to its a-textual interpretation of the CBE regulation under *Auer v. Robbins*, 519 U.S. 452 (1997). But "*Auer* deference is warranted only when the language of the regulation is ambiguous." *Christensen v. Harris County*, 529 U.S. 576, 588 (2000). The CBE regulation unambiguously permits labeling changes without requiring them to be based on "new" information. This Court therefore owes no deference to, and must reject, the government's effort to import a new-information limitation into the regulation through "interpretation."[26] A contrary approach

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[25] The government misses the point in disputing (at 32) whether that provision indicates congressional intent to preserve state-law remedies. The clause plainly evidences Congress's belief that drug manufacturers should "maintain" their labeling in accordance with the CBE regulation – which refutes Wyeth's claim that manufacturers cannot change their labeling to strengthen a warning in light of a state-law duty or judgment.

[26] *See also Norfolk Southern Ry. Co. v. Shanklin*, 529 U.S. 344, 356 (2000) (agency's interpretation must be rejected when

would permit the agency functionally to amend its regulations without complying with Administrative Procedure Act ("APA") notice-and-comment procedures. *See Shalala v. Guernsey Mem'l Hosp.*, 514 U.S. 87, 100 (1995) (noting that an "APA rulemaking" would be required if an interpretive rule "adopted a new position inconsistent with" any "existing regulations"). Indeed, FDA's lack of confidence in its litigating position is reflected in the recent issuance of notice-and-comment rulemaking to implement its new view that CBE supplements can be based only on "new information." *See* 73 Fed. Reg. 2848 (2008).

Furthermore, to the extent Wyeth argues that a CBE supplement must be based on information about a *newly discovered risk* – as opposed to a manufacturer's reevaluation or analysis of existing risk information – that position conflicts with the FDA's own proposal to codify its "new information" limitation on the CBE regulation. The proposed rule defines "newly acquired information" to include "new analyses of *previously submitted* data." *Id.* at 2853 (emphasis added). Thus, even under FDA's proposed rule (which the government asserts reflects FDA's view of the meaning of the current CBE regulation), Wyeth could have re-analyzed data on the safety of IV-push injection and used the CBE regulation to implement a stronger warning or instruction.

Congress's recent amendments to the FDCA comport with that understanding of what information

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it is "inconsistent with the text" of the regulation). Courts of appeals have repeatedly refused to adopt agency interpretations that, like FDA's new interpretation of the CBE regulation, clash with the rule's text. *See, e.g., United States v. Hoyts Cinemas Corp.*, 380 F.3d 558, 569 (1st Cir. 2004); *Fina Oil & Chem. Co. v. Norton*, 332 F.3d 672, 676 (D.C. Cir. 2003); *Dithiocarbamate Task Force v. EPA*, 98 F.3d 1394, 1399 (D.C. Cir. 1996).

can be considered "new" in the context of a labeling change. The 2007 Amendments provide FDA with limited authority to order labeling changes based on "new safety information," § 901(a), 121 Stat. 924 (codified at 21 U.S.C. § 355(*o*)(4)(A)), which is defined to include "scientific data" about "a serious risk or an unexpected serious risk associated with use of the drug that the Secretary has become aware of *(that may be based on a new analysis of existing information)* since the drug was approved," § 901(b), 121 Stat. 927-28 (emphasis added) (codified at 21 U.S.C. § 355-1(b)(3)(A)). Thus, Congress too has recognized that, because risk information about a drug builds up over time, it makes no sense to limit labeling changes to those based wholly on information not available when the agency last considered the labeling. *See* Karen E. Lasser et al., *Timing of New Black Box Warnings and Withdrawals for Prescription Medications*, 287 J.A.M.A. 2215, 2218-19 (May 1, 2002) (providing examples of drugs that were withdrawn from the market based on adverse effects that had appeared in pre-market trials).

In revising the CBE regulation in 1985, FDA recognized that reevaluation of existing data can support a CBE supplement. In 1982, FDA had proposed revising the CBE regulation to remove the clause allowing manufacturers to "delete false, misleading, or unsupported indications for use or claims for effectiveness" through a CBE supplement. In response, a commenter "urged" FDA to continue to permit applicants "to delete, without prior approval, any indication for use or claim for effectiveness considered by the applicant to be unsupportable *as a result of the applicant's reconsideration of the data* or considered by the applicant to present an unacceptable

safety to efficacy ratio." 50 Fed. Reg. 7452, 7469 (1985) (emphasis added). In the 1985 final rule, FDA stated that it "agree[d] with" that comment and revised the final rule accordingly. *Id.*

Further, in the same 1982 document on which Wyeth (at 37) and the government (at 22) rely, FDA proposed a number of provisions containing an explicit "new information" limitation.[27] Those proposals demonstrate that FDA knew how to limit the effect of its regulations to cases of new information when it wanted to.[28] Finally, despite its newfound interpretation of the regulation, the government provides no indication that FDA has ever rejected

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[27] *See* 47 Fed. Reg. 46,622, 46,652 (1982) (proposing a requirement that drug companies submit an annual report containing, among other things, a "brief summary of significant *new information* from the previous year that might affect the safety, effectiveness, or labeling of the drug product") (proposed 21 C.F.R. § 314.80(c)(4)(i)) (emphasis added); *id.* at 46,657 (proposing provision that FDA would notify drug company that it intended to withdraw approval of drug if it found, in part on "basis of *new information* before FDA," that drug no longer meets criteria for approval) (proposed 21 C.F.R. § 314.150(a)(2)(iii)) (emphasis added); *id.* (proposed 21 C.F.R. § 314.150(b)(2)) (same); *id.* (proposed 21 C.F.R. § 314.150(b)(3)) (same). Although, as Wyeth and the government note, FDA there indicated that one use for the CBE regulation would be to add warnings about new information, it did not say the regulation applied *only* to changes based on such information. *See id.* at 46,623, 46,635.

[28] Although Wyeth also argues (at 35) that FDA lacks statutory authority to promulgate a rule permitting drug manufacturers to alter their labels without prior FDA approval based on anything other than newly discovered information, the government does not adopt that argument and, instead, observes (at 3 n.1) that the statute is silent on changes to the labeling in an approved new-drug application.

CBE supplements for failing to comply with the "new information" requirement it now posits.[29]

C. Wyeth Can Comply With The Vermont Judgment Without Changing Its Label

Ms. Levine did not seek or obtain an injunction. Wyeth could pay her damages award without changing Phenergan's labeling. Its violation of state-law duties might induce, but does not mandate, future corrective action, and such inducement does not create an actual conflict with federal law. *Cf. Bates*, 544 U.S. at 445 (explaining that "an event, such as a jury verdict, that merely motivates an optional decision is not a requirement").

This Court's cases show that, for preemption purposes, common law is distinct from statutory and regulatory law because it fulfills primarily a compensatory function, rather than a regulatory one. As the Court recognized in *Sprietsma*, "common-law claims" – "unlike most administrative and legislative regulations" – "necessarily perform an important remedial role in compensating accident victims." 537 U.S. at 64. And, in *Goodyear Atomic Corp. v. Miller*, 486 U.S. 174 (1988), the Court explained that a workers' compensation award has only "incidental regulatory effects" that are "significantly" less "intrusive" than "direct state regulation," such as a state statute. *Id.*

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[29] Wyeth, which bore the burden of establishing its preemption defense, never argued at trial that the CBE regulation applied only to changes based on "new information"; nor did it object to a jury instruction lacking any mention of that limitation. JA223, 228. Before preemption could definitively be found, therefore, a remand would be required to determine whether Wyeth waived or forfeited that argument under state law and, if not, whether the evidence supports a CBE supplement under the new standard.

at 185; *see also Silkwood*, 464 U.S. at 249, 256 (while federal law occupies field of nuclear-safety regulation, state tort law can provide damages remedy for those injured in nuclear incidents).[30]

This Court has recognized, but not resolved, the question whether the incidental regulatory effects of state tort judgments create preemptive "obstacles" to the accomplishment of federal purposes. *See Geier*, 529 U.S. at 882. There can be no doubt, however, that there is no physical impossibility, because Wyeth could pay the judgment to Ms. Levine and not otherwise alter its conduct.

Wyeth relies heavily on *Riegel*'s statement that "common-law liability is premised on the existence of a legal duty, and a tort judgment therefore establishes that the defendant has violated a state-law obligation." 128 S. Ct. at 1008 (internal quotation marks omitted). But *Riegel* did not say that, to comply with a state-law judgment, the defendant needed to do more than pay damages. Rather, it held that Congress intended the term "requirements" to encompass those state-law duties that, when violated, lead to damages claims. Significantly, by creating clarity for Congress's future usage of the term "requirements" in express preemption provisions, *id.*,

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[30] The other cases on which Wyeth relies (at 33) are inapposite. *Geier v. American Honda Motor Co.*, 529 U.S. 861 (2000), did not involve the physical-impossibility test, but rather addressed whether a state tort suit posed an "obstacle" to a "deliberately imposed" federal requirement. *Id.* at 881. *Buckman* involved "[s]tate-law fraud-on-the-FDA claims." 531 U.S. at 350. Wyeth does not assert that the claims here fall into that category. The Court emphasized that the fraud claims in *Buckman* arose "solely from the violation of FDCA requirements" and distinguished cases (like this one) based on "traditional state tort law principles." *Id.* at 352-53.

Riegel did not purport to announce a rule for *implied* preemption cases. It would be anomalous to suppose that *implied* preemption operates the same way as when Congress enacts an *express* preemption provision using the term "requirements." Yet that is the logical import of Wyeth's argument.

III. THE VERMONT JUDGMENT POSES NO OBSTACLE TO THE FEDERAL REGIME

A. Vermont Law Complements The Federal Regime

1. Vermont law imposes a duty to warn on drug manufacturers that complements and parallels the FDCA's duties. Under Vermont law, drug companies must "provide adequate instructions about how to use the product safely." JA228. *See also Restatement (Third) of Torts: Products Liability* § 6(a), (b)(3), (d)(2). That duty requires courts to assess "the seriousness of the risk to patients" and "the likelihood or incidence of injury," JA229, using a similar standard as the federal misbranding provision, 21 U.S.C. § 352(f).[31] *See supra* pp. 26-27.

Thus, both state and federal law require drug manufacturers to provide physicians with information about the known risks of their products. As recently as 1998, FDA recognized the complementary nature of those duties, stating that it "does not believe that the evolution of state tort law will cause the development of standards that would be at odds with the agency's regulations." 63 Fed. Reg. 66,378, 66,384 (1998). In both *Bates* and *Lohr*, the Court held that the existence of federal labeling rules did not, without more, deny states "'the right to provide a traditional damages remedy for violations of

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[31] Wyeth did not object to these jury instructions. JA223.

common-law duties'" that "'parallel federal requirements.'" *Bates*, 544 U.S. at 447 (quoting *Lohr*, 518 U.S. at 495). Although "the threat of a damages remedy will give manufacturers an additional cause to comply" with federal rules, that does not make such suits obstacles to federal purposes. *Id.* at 448.

On the contrary, Vermont law furthers the FDCA's "high purpose" of "protect[ing] consumers," *Kordel*, 335 U.S. at 349, by holding drug companies liable when they fail to provide physicians with adequate information about their products' risks. In carrying out its paramount mission of "protect[ing] the public health by ensuring that . . . drugs are safe and effective," 21 U.S.C. § 393(b)(2)(B), FDA requires drug companies to revise inadequate labeling (which may include seeking agency approval of labeling changes even in the absence of an agency demand). Under FDA regulations, drug companies must revise drug labeling to include a warning "*as soon as* there is *reasonable evidence* of an association of a serious hazard with a drug; *a causal relationship need not have been proved*." 21 C.F.R. § 201.80(e) (emphases added).

Thus, like the federal scheme at issue in *Bates*, the FDCA, as implemented by FDA, "contemplates that [drug] labels will evolve over time, as manufacturers gain more information about their products' performance in diverse settings." 544 U.S. at 451. As *Bates* recognized, "tort suits can serve as a catalyst in this process," because such actions "'may provide manufacturers with added dynamic incentives to continue to keep abreast of all possible injuries stemming from use of their product'" and thereby prompt necessary labeling changes. *Id.* (quoting *Ferebee v. Chevron Chem. Co.*, 736 F.2d 1529, 1541-42 (D.C. Cir. 1984)).

The common-law regulatory-compliance defense, which permits manufacturers to present evidence of compliance with federal law in defending against failure-to-warn suits, presents another way in which tort law complements the federal regulatory scheme. Here, the trial court instructed the jury – without objection – that it could "consider evidence of compliance by Wyeth with FDA requirements in obtaining approval for the Phenergan warning." JA227. *See also Restatement (Third) of Torts: Products Liability* § 4(b).

In this case, Wyeth not only presented a vigorous regulatory-compliance defense, but also attempted to bolster that defense with evidence showing the benefits of IV-push injection of Phenergan. That evidence, however, amounted to nothing more than speculation that IV-push administration might theoretically be medically appropriate in some rare and dire circumstance. *See supra* p. 16. Neither Wyeth nor its *amici* suggest in this Court any benefits of IV-push injection of Phenergan that Wyeth neglected to introduce at trial. Nor do they assert that such a benefit, if one existed, could outweigh the grave risk of gangrene and amputation they concede may result from IV-push injection. For any rational person, a greatly increased risk of amputation for minutes-faster relief from nausea is never a risk worth taking. Wyeth's failure to prevail below thus cannot be blamed on the trial court's ignorance either of FDA's regulation of Phenergan's labeling or of any (hypothetical) "'patients who reaped [the] benefits'" of IV-push injection of Phenergan. Wyeth Br. 46 (quoting *Riegel*, 128 S. Ct. at 1008). Rather, the jury properly determined that FDA never considered (and could not have concluded) that IV push would benefit any

actual patient, as compared to IV drip, which the record showed had a significantly lower risk of causing gangrene.[32]

2. Failure-to-warn suits augment the FDCA regime by encouraging manufacturers to provide FDA with data and analyses on risks of drugs.

Manufacturers conduct relatively limited clinical trials to support applications to market new drugs; FDA *does not test* drugs.[33] Because the participants are healthy adults, the trials do not reveal adverse reactions affecting, for example, pregnant, elderly, or sick patients, and, because of their relatively brief durations, the studies also do not uncover side effects with long latency periods. *See* Institute of Medicine Report 37-38. Unsurprisingly, a 1990 GAO report found that serious post-approval risks surfaced in more than half of the drugs FDA approved between 1976 and 1985.[34]

After FDA has approved a drug with manufacturer-proposed labeling, the manufacturer bears primary responsibility for analyzing safety information and evaluating needed labeling modifications in response to that information. *See* 21 C.F.R. §§ 201.80(e), 314.80(b). FDA's post-approval authority is limited,

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[32] Wyeth presented no evidence at trial and makes no argument in this Court that Ms. Levine's medical condition was so dire as to warrant the risks she incurred.

[33] Institute of Medicine of the National Academies, *The Future of Drug Safety: Promoting and Protecting the Health of the Public* 34-38, 152 (2007) ("Institute of Medicine Report").

[34] U.S. General Accounting Office, Report to the Chairman, Subcomm. on Human Resources and Intergovernmental Relations, Comm. on Government Operations, House of Representatives, *FDA Drug Review: Postapproval Risks 1976-85*, at 3 (Apr. 1990).

however – particularly prior to 2007, when FDA could not force a manufacturer to make a labeling change. Instead, the agency "negotiated" such changes with the manufacturer, as the record here shows occurred with Wyeth. *See supra* p. 8. Although most risks of a drug will become known or fully appreciated only *after* FDA approves the drug, the post-approval period is when FDA's regulatory powers are most limited. State-law actions therefore induce manufacturers to evaluate and act on risk information they receive.

Throughout FDA's history, well-respected independent observers have recognized that the agency lacks the resources and tools to serve as the sole protector of public health. In 1955, the year FDA allowed Wyeth to market Phenergan, an FDA advisory committee found that the "budget and staff of [FDA] are inadequate to permit the discharge of its existing responsibilities for the protection of the American public."[35] Three recent studies have expressed similar doubts about FDA's abilities and performance. In 2007, an FDA Science Board subcommittee "concluded that science at the FDA is in a precarious position: the Agency suffers from serious scientific deficiencies and is not positioned to meet current or emerging regulatory responsibilities."[36] "FDA's inability to keep up with scientific advances," the report explained, "means that *American lives are at risk*." FDA Science Board Report 3 (emphasis added). The National

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[35] Citizens Advisory Committee on the Food and Drug Administration, Report to the Secretary of Health, Education and Welfare, H.R. Doc. No. 84-227, at 53 (1955).

[36] FDA Science Board, *Report of the Subcommittee on Science and Technology: FDA Science and Mission at Risk* 2 (Nov. 2007) ("FDA Science Board Report").

Academy of Sciences' Institute of Medicine and the Government Accountability Office issued reports, in 2007 and 2006, respectively, finding that deficiencies in the drug safety system directly affected the quality of risk information provided to the public. *See* Institute of Medicine Report 4; GAO Drug Safety Report 5. Those recent studies further undermine the notion that state-law remedial suits pose an obstacle to FDA's efforts to regulate the pharmaceutical industry.

B. Wyeth's Obstacle-Preemption Arguments Have No Merit

Despite the parallel objectives of federal and state law and the long history of litigation against drug manufacturers, Wyeth and the government contend that the Vermont judgment poses an obstacle to the federal scheme. They claim FDA comprehensively regulates the content of a drug's labeling and carefully balances risks and benefits in determining what information should appear on that labeling and how the information should be expressed. Wyeth further asserts that FDA performed a careful and complete balancing with respect to the risk at issue in this case, while the government claims it is irrelevant whether such balancing took place, so long as the agency was aware of the "relevant risk," broadly defined – that is, the general risk of arterial exposure to Phenergan, not the risk of IV-push administration specifically. Those contentions caricature the federal scheme, overlook the complementary role state tort law has long played in that regime, and ignore that the record and findings of the Vermont courts below establish that FDA never performed a balancing of the risks and supposed benefits of IV-push administration of Phenergan.

1. The assertion that FDA "balances" what warnings and instructions should appear in a drug's labeling is incorrect. Like Vermont law, federal law requires manufacturers to warn of *all* known risks of a drug. *See* 21 U.S.C. § 352(f); 21 C.F.R. § 201.80(e). As FDA has explained, "it is essential to the safe use of a drug for the physician to know *all* adverse reactions that are likely to occur with it," and "the act requires labeling to include warnings about both potential and verified hazards." 44 Fed. Reg. at 37,443, 37,447 (emphasis added). In FDA's view, "practicing physicians will welcome such information so that they can make their best informed medical judgments in the care of their patients." *Id.* Thus, nothing in the statute or regulations empowers FDA to permit a manufacturer to withhold information about a substantiated risk (such as the greatly increased risk of inadvertent arterial exposure leading to gangrene through IV-push injection of Phenergan) on the ground that providing such information might deter beneficial uses of the drug.

2. In any event, there is no evidence that FDA determined that Wyeth adequately informed medical practitioners of the specific risks of IV-push injection of Phenergan. The Vermont Supreme Court found that the "record lacks any evidence" that FDA would have "prohibited the use of a stronger warning with respect to IV-push administration of Phenergan." Pet. App. 16a. "Neither the letters [Wyeth and FDA exchanged] nor any other evidence presented to the jury indicated that the FDA wished to preserve the use of IV push as a method of administering Phenergan." *Id.* at 17a; *see also id.* at 18a n.2;

JA249.[37] Thus, this case does not involve a claim that Wyeth failed to include in labeling "a statement that FDA has considered and found scientifically unsubstantiated," 71 Fed. Reg. 3922, 3935 (2006), as the government implicitly concedes.

Wyeth argues (at 43-45), however, that FDA's 1997 letter to Wyeth embodies a conscious resolution of the issue in this case. But that letter, which came approximately 16 years after Wyeth submitted the supplemental application in question, contains no indication that FDA considered whether the risks of IV-push injection of Phenergan merited a stronger warning or an instruction precluding that method of administration. Indeed, FDA's letter did not insist on revised warnings regarding the risks of arterial exposure that FDA itself originally had suggested, apparently because it "viewed the change as non-substantive and rejected it for formatting reasons." U.S. Br. 25. FDA's 1997 letter therefore is a far cry from "an expert judgment" (Wyeth Br. 46) that any benefit of IV-push injection outweighs its risks or that a stronger warning would deter beneficial IV-push injections.

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[37] Although Wyeth's obstacle claim focuses on FDA's purported decision to permit "IV administration of Phenergan," Wyeth Br. 40, 46, the state-law duty imposed by Vermont's highest court on review here is premised on the label's failure to have proper warnings or instructions regarding *IV-push* administration. *See, e.g.*, Pet. App. 3a. That understanding controls here. *See Perez v. Campbell*, 402 U.S. 637, 644 (1971) (in determining conflict preemption, the Court is "bound by" the state's highest court's interpretation of state law); *see also Riley v. Kennedy*, 128 S. Ct. 1970, 1985 (2008) ("A State's highest court is unquestionably 'the ultimate exposito[r] of state law.'") (quoting *Mullaney v. Wilbur*, 421 U.S. 684, 691 (1975)) (alteration in original).

This case is therefore quite unlike *Geier*, on which Wyeth (at 47-49) and the government (at 18) rely. There, the Court found that a suit premised on an automaker's failure to install airbags actually conflicted with a federal regulation that did not require airbags in all circumstances. *See* 529 U.S. at 874-81. Unlike in this case, the agency in *Geier* specifically "had *rejected*" a proposed "'all airbag' standard" and instead imposed a standard that "deliberately" sought "a mix of several different passive restraint systems." *Id.* at 878-79.[38]

This case more closely resembles *Sprietsma*. There, a damages action premised on a boat manufacturer's failure to install a propeller guard was not preempted where the federal agency considered whether to require such guards but ultimately took no action on the topic. *See* 537 U.S. at 60-62, 65-67. Indeed, this case presents an even weaker argument for conflict preemption than *Sprietsma*, because FDA did not even consider, let alone reject or take no action on, stronger warnings or instructions regarding IV-push injection.[39]

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[38] *See also Lohr*, 518 U.S. at 501 (distinguishing case in which "the Federal Government has weighed the competing interests relevant to the particular requirement in question, reached an unambiguous conclusion about how those competing considerations should be resolved in a particular case or set of cases, and implemented that conclusion via a specific mandate on" manufacturer).

[39] Because FDA made no judgment on the labeling deficiency at issue in this case, the Court can reject Wyeth's preemption claim without considering whether FDA action on a manufacturer's labeling proposal in a supplemental application – which is not explained in a written order and generally is not subject to judicial review – should ever be given preemptive effect. (The administrative orders at issue in *Geier* and *Riegel*, by contrast,

For its part, the government asserts that state-law claims are preempted so long as the manufacturer informed the agency of the "relevant risk," which the government describes as inadvertent arterial exposure causing gangrene. U.S. Br. 25. But that overly broad position would abolish any form of compensation for nearly all patients injured by FDA-approved drugs because it would support preemption whenever the manufacturer can point to some bit of data regarding the risk in its submissions to the agency, without any showing that FDA considered or made a judgment about what the labeling should say regarding the risk. The government's new position also ignores that the labeling deficiency demonstrated at trial was not a failure to warn that inadvertent arterial exposure would cause gangrene. Rather, Wyeth failed either to warn that IV-push injection has a far greater risk of inadvertent arterial exposure or to preclude that method of administration altogether. It cannot be enough to inform the agency of a side effect, without also disclosing that the side effect occurs much more frequently with one method of administration than another.[40]

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were subject to judicial review. *See* 15 U.S.C. § 1392(b) (1982) (authorizing judicial review of "orders establishing, amending, or revoking a Federal motor vehicle safety standard"); 21 U.S.C. § 360g(a)(4) (providing for judicial review of an order approving an application to market a medical device).)

[40] Because the Vermont judgment in this case poses no obstacle to the federal regime, the Court need not address Wyeth's criticisms of the Vermont Supreme Court's discussion of the effect of § 202 of the 1962 Amendments.

C. FDA's Inconsistent Position Is Entitled To No Weight

This Court should give no weight to FDA's opinion, expressed in a regulatory preamble and an *amicus* brief in this case, that federal law generally preempts state failure-to-warn claims. "It is not certain that an agency regulation determining the preemptive effect of *any* federal statute is entitled to deference," *Lohr*, 518 U.S. at 512 (O'Connor, J., concurring in part and dissenting in part), much less agency pronouncements of the types presented here. Even assuming it is, the extent of that consideration would depend on the persuasiveness of the agency's views and their consistency with past agency positions (as the government concedes (at 26)). *See Skidmore*, 323 U.S. at 140; *see also United States v. Mead Corp.*, 533 U.S. 218, 228 (2001); *Good Samaritan Hosp. v. Shalala*, 508 U.S. 402, 417 (1993); *cf. Riegel*, 128 S. Ct. at 1009. This is particularly true where the agency takes inconsistent positions on the preemptive effect of a federal regime. *See Bates*, 544 U.S. at 449 (describing government's preemption argument as "particularly dubious" given agency's change in position).

FDA's position is not consistent, grounded in any statutory change, or persuasive. Rather, "FDA's current view of the preemptive effect of its labeling regulations is a 180-degree reversal of its prior position." *In re Bextra and Celebrex Mktg. Sales Practices & Prod. Liab. Litig.*, No. M:05-1699 CRB, 2006 WL 2374742, at *8 (N.D. Cal. Aug. 16, 2006).[41] For

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[41] *Accord* Entry on Pl.'s Mot. To Reconsider at 13, *Tucker v. SmithKline Beecham Corp.*, No. 1:04-cv-1748-DFH-WTL (S.D. Ind. July 18, 2008) ("FDA's current position on preemption is not long standing but is in fact a 180-degree reversal from its

example, contrary to FDA's current view that its labeling regulations impose a "ceiling" on the amount of information the public should receive, when it established requirements for patient labeling for selected prescription drugs in 1998, FDA stated that its "regulations establish the *minimal standards* necessary, but were not intended to preclude the states from imposing additional labeling requirements." 63 Fed. Reg. at 66,384 (emphasis added). Congress enacted no intervening statute to justify that shift. And, when FDA proposed the revised labeling rule (to which it later appended its preamble advocating preemption), the agency stated that the "proposed rule does not preempt State law." 65 Fed. Reg. 81,082, 81,103 (2000). On numerous occasions, "FDA [has] recognize[d] that product liability plays an important role in consumer protection." 59 Fed. Reg. 3944, 3948 (1994).[42] Its current policy, which represents a reversal of that longstanding position, has no basis in any change in law.

* * *

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earlier stance.") (internal quotation marks omitted); *see also* 2 James T. O'Reilly, *Food and Drug Administration* § 26.56 (3d ed. 2007) (describing FDA's change in position).

[42] *See also, e.g.*, Margaret Jane Porter, *The Lohr Decision: FDA Perspective and Position*, 52 Food & Drug L.J. 7, 11 (1997) (FDA's then-Chief Counsel explained that, if the Medical Device Amendments were interpreted to preempt state-law claims, "FDA's regulation of devices would have been accorded an entirely different weight in private tort litigation than its counterpart regulation of drugs and biologics").

Diana Levine needlessly lost her arm and her livelihood from an unnecessarily dangerous method of administering a drug intended to relieve nausea. Wyeth never made FDA aware that IV-push injection greatly increased the risks of gangrene, and its Phenergan labeling similarly omitted any warning of those risks. Vermont's duty to warn of such risks is perfectly consistent with federal law and promotes Congress's paramount interest in ensuring safe use of drugs.

CONCLUSION

The judgment of the Vermont Supreme Court should be affirmed.

Respectfully submitted,

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ADDENDUM

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21 U.S.C. § 321. Definitions; generally

For the purposes of this chapter—

* * *

(p) The term "new drug" means—

(1) Any drug (except a new animal drug or an animal feed bearing or containing a new animal drug) the composition of which is such that such drug is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof, except that such a drug not so recognized shall not be deemed to be a "new drug" if at any time prior to June 25, 1938, it was subject to the Food and Drugs Act of June 30, 1906, as amended, and if at such time its labeling contained the same representations concerning the conditions of its use; or

(2) Any drug (except a new animal drug or an animal feed bearing or containing a new animal drug) the composition of which is such that such drug, as a result of investigations to determine its safety and effectiveness for use under such conditions, has become so recognized, but which has not, otherwise than in such investigations, been used to a material extent or for a material time under such conditions.

* * *

21 U.S.C. § 331. Prohibited acts

The following acts and the causing thereof are prohibited:

(a) The introduction or delivery for introduction into interstate commerce of any food, drug, device, or cosmetic that is adulterated or misbranded.

(b) The adulteration or misbranding of any food, drug, device, or cosmetic in interstate commerce.

(c) The receipt in interstate commerce of any food, drug, device, or cosmetic that is adulterated or misbranded, and the delivery or proffered delivery thereof for pay or otherwise.

(d) The introduction or delivery for introduction into interstate commerce of any article in violation of section 344, 355, or 360bbb-3 of this title.

* * *

21 U.S.C. § 332. Injunction proceedings

(a) Jurisdiction of courts

The district courts of the United States and the United States courts of the Territories shall have jurisdiction, for cause shown[1] to restrain violations of section 331 of this title, except paragraphs (h), (i), and (j).

(b) Violation of injunction

In case of violation of an injunction or restraining order issued under this section, which also constitutes a violation of this chapter, trial shall be by the court, or, upon demand of the accused, by a jury.

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[1] So in original. Probably should have a comma.

21 U.S.C. § 333. Penalties

(a) Violation of section 331 of this title; second violation; intent to defraud or mislead

(1) Any person who violates a provision of section 331 of this title shall be imprisoned for not more than one year or fined not more than $1,000, or both.

(2) Notwithstanding the provisions of paragraph (1), if any person commits such a violation after a conviction of him under this section has become final, or commits such a violation with the intent to defraud or mislead, such person shall be imprisoned for not more than three years or fined not more than $10,000, or both.

* * *

21 U.S.C. § 334. Seizure

(a) Grounds and jurisdiction

(1) Any article of food, drug, or cosmetic that is adulterated or misbranded when introduced into or while in interstate commerce or while held for sale (whether or not the first sale) after shipment in interstate commerce, or which may not, under the provisions of section 331(*ll*), 344, or 355 of this title, be introduced into interstate commerce, shall be liable to be proceeded against while in interstate commerce, or at any time thereafter, on libel of information and condemned in any district court of the United States or United States court of a Territory within the jurisdiction of which the article is found. No libel for condemnation shall be instituted under this chapter, for any alleged misbranding if there

is pending in any court a libel for condemnation proceeding under this chapter based upon the same alleged misbranding, and not more than one such proceeding shall be instituted if no such proceeding is so pending, except that such limitations shall not apply (A) when such misbranding has been the basis of a prior judgment in favor of the United States, in a criminal, injunction, or libel for condemnation proceeding under this chapter, or (B) when the Secretary has probable cause to believe from facts found, without hearing, by him or any officer or employee of the Department that the misbranded article is dangerous to health, or that the labeling of the misbranded article is fraudulent, or would be in a material respect misleading to the injury or damage of the purchaser or consumer. In any case where the number of libel for condemnation proceedings is limited as above provided the proceeding pending or instituted shall, on application of the claimant, seasonably made, be removed for trial to any district agreed upon by stipulation between the parties, or, in case of failure to so stipulate within a reasonable time, the claimant may apply to the court of the district in which the seizure has been made, and such court (after giving the United States attorney for such district reasonable notice and opportunity to be heard) shall by order, unless good cause to the contrary is shown, specify a district of reasonable proximity to the claimant's principal place of business, to which the case shall be removed for trial.

(2) The following shall be liable to be proceeded against at any time on libel of information and condemned in any district court of the United States or United States court of a Territory within the jurisdiction of which they are found: (A) Any drug that

is a counterfeit drug, (B) Any container of a counterfeit drug, (C) Any punch, die, plate, stone, labeling, container, or other thing used or designed for use in making a counterfeit drug or drugs, and (D) Any adulterated or misbranded device.

(3)(A) Except as provided in subparagraph (B), no libel for condemnation may be instituted under paragraph (1) or (2) against any food which—

(i) is misbranded under section 343(a)(2) of this title because of its advertising, and

(ii) is being held for sale to the ultimate consumer in an establishment other than an establishment owned or operated by a manufacturer, packer, or distributor of the food.

(B) A libel for condemnation may be instituted under paragraph (1) or (2) against a food described in subparagraph (A) if—

(i)(I) the food's advertising which resulted in the food being misbranded under section 343(a)(2) of this title was disseminated in the establishment in which the food is being held for sale to the ultimate consumer,

(II) such advertising was disseminated by, or under the direction of, the owner or operator of such establishment, or

(III) all or part of the cost of such advertising was paid by such owner or operator; and

(ii) the owner or operator of such establishment used such advertising in the establishment to promote the sale of the food.

(b) Procedure; multiplicity of pending proceedings

The article, equipment, or other thing proceeded against shall be liable to seizure by process pursuant to the libel, and the procedure in cases under this section shall conform, as nearly as may be, to the procedure in admiralty; except that on demand of either party any issue of fact joined in any such case shall be tried by jury. When libel for condemnation proceedings under this section, involving the same claimant and the same issues of adulteration or misbranding, are pending in two or more jurisdictions, such pending proceedings, upon application of the claimant seasonably made to the court of one such jurisdiction, shall be consolidated for trial by order of such court, and tried in (1) any district selected by the claimant where one of such proceedings is pending; or (2) a district agreed upon by stipulation between the parties. If no order for consolidation is so made within a reasonable time, the claimant may apply to the court of one such jurisdiction and such court (after giving the United States attorney for such district reasonable notice and opportunity to be heard) shall by order, unless good cause to the contrary is shown, specify a district of reasonable proximity to the claimant's principal place of business, in which all such pending proceedings shall be consolidated for trial and tried. Such order of consolidation shall not apply so as to require the removal of any case the date for trial of which has been fixed. The court granting such order shall give prompt notification thereof to the other courts having jurisdiction of the cases covered thereby.

* * *

21 U.S.C. § 352. Misbranded drugs and devices

A drug or device shall be deemed to be misbranded—

(a) False or misleading label

If its labeling is false or misleading in any particular. Health care economic information provided to a formulary committee, or other similar entity, in the course of the committee or the entity carrying out its responsibilities for the selection of drugs for managed care or other similar organizations, shall not be considered to be false or misleading under this paragraph if the health care economic information directly relates to an indication approved under section 355 or under section 262(a) of Title 42 for such drug and is based on competent and reliable scientific evidence. The requirements set forth in section 355(a) of this title or in section 262(a) of Title 42 shall not apply to health care economic information provided to such a committee or entity in accordance with this paragraph. Information that is relevant to the substantiation of the health care economic information presented pursuant to this paragraph shall be made available to the Secretary upon request. In this paragraph, the term "health care economic information" means any analysis that identifies, measures, or compares the economic consequences, including the costs of the represented health outcomes, of the use of a drug to the use of another drug, to another health care intervention, or to no intervention.

* * *

(f) Directions for use and warnings on label

Unless its labeling bears (1) adequate directions for use; and (2) such adequate warnings against use in those pathological conditions or by children where its use may be dangerous to health, or against unsafe dosage or methods or duration of administration or application, in such manner and form, as are necessary for the protection of users, except that where any requirement of clause (1) of this paragraph, as applied to any drug or device, is not necessary for the protection of the public health, the Secretary shall promulgate regulations exempting such drug or device from such requirement. Required labeling for prescription devices intended for use in health care facilities or by a health care professional and required labeling for in vitro diagnostic devices intended for use by health care professionals or in blood establishments may be made available solely by electronic means, provided that the labeling complies with all applicable requirements of law, and that the manufacturer affords such users the opportunity to request the labeling in paper form, and after such request, promptly provides the requested information without additional cost.

* * *

21 U.S.C. § 355. New drugs

(a) Necessity of effective approval of application

No person shall introduce or deliver for introduction into interstate commerce any new drug, unless an approval of an application filed pursuant to subsection (b) or (j) of this section is effective with respect to such drug.

(b) Filing application; contents

(1) Any person may file with the Secretary an application with respect to any drug subject to the provisions of subsection (a) of this section. Such person shall submit to the Secretary as a part of the application (A) full reports of investigations which have been made to show whether or not such drug is safe for use and whether such drug is effective in use; (B) a full list of the articles used as components of such drug; (C) a full statement of the composition of such drug; (D) a full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug; (E) such samples of such drug and of the articles used as components thereof as the Secretary may require; (F) specimens of the labeling proposed to be used for such drug. The applicant shall file with the application the patent number and the expiration date of any patent which claims the drug for which the applicant submitted the application or which claims a method of using such drug and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug. If an application is filed under this subsection for a drug and a patent which claims such drug or a method of using such drug is issued after the filing

date but before approval of the application, the applicant shall amend the application to include the information required by the preceding sentence. Upon approval of the application, the Secretary shall publish information submitted under the two preceding sentences. The Secretary shall, in consultation with the Director of the National Institutes of Health and with representatives of the drug manufacturing industry, review and develop guidance, as appropriate, on the inclusion of women and minorities in clinical trials required by clause (A), and (G) any assessments required under section 355c of this title.

* * *

(c) Period for approval of application; period for, notice, and expedition of hearing; period for issuance of order

(1) Within one hundred and eighty days after the filing of an application under subsection (b) of this section, or such additional period as may be agreed upon by the Secretary and the applicant, the Secretary shall either—

(A) Approve the application if he then finds that none of the grounds for denying approval specified in subsection (d) of this section applies, or

(B) Give the applicant notice of an opportunity for a hearing before the Secretary under subsection (d) of this section on the question whether such application is approvable. If the applicant elects to accept the opportunity for hearing by written request within thirty days after such notice, such hearing shall commence not more than ninety days after the expiration of such thirty days unless the Secretary and the applicant otherwise agree. Any

such hearing shall thereafter be conducted on an expedited basis and the Secretary's order thereon shall be issued within ninety days after the date fixed by the Secretary for filing final briefs.

* * *

(d) Grounds for refusing application; approval of application; "substantial evidence" defined

If the Secretary finds, after due notice to the applicant in accordance with subsection (c) of this section and giving him an opportunity for a hearing, in accordance with said subsection, that (1) the investigations, reports of which are required to be submitted to the Secretary pursuant to subsection (b) of this section, do not include adequate tests by all methods reasonably applicable to show whether or not such drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof; (2) the results of such tests show that such drug is unsafe for use under such conditions or do not show that such drug is safe for use under such conditions; (3) the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug are inadequate to preserve its identity, strength, quality, and purity; (4) upon the basis of the information submitted to him as part of the application, or upon the basis of any other information before him with respect to such drug, he has insufficient information to determine whether such drug is safe for use under such conditions; or (5) evaluated on the basis of the information submitted to him as part of the application and any other information before him with respect to such drug, there is a lack of substantial evidence that the drug will have the effect it purports or is represented

to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling thereof; or (6) the application failed to contain the patent information prescribed by subsection (b) of this section; or (7) based on a fair evaluation of all material facts, such labeling is false or misleading in any particular; he shall issue an order refusing to approve the application. If, after such notice and opportunity for hearing, the Secretary finds that clauses (1) through (6) do not apply, he shall issue an order approving the application. As used in this subsection and subsection (c) of this section, the term "substantial evidence" means evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof. If the Secretary determines, based on relevant science, that data from one adequate and well-controlled clinical investigation and confirmatory evidence (obtained prior to or after such investigation) are sufficient to establish effectiveness, the Secretary may consider such data and evidence to constitute substantial evidence for purposes of the preceding sentence.

(e) Withdrawal of approval; grounds; immediate suspension upon finding imminent hazard to public health

The Secretary shall, after due notice and opportunity for hearing to the applicant, withdraw approval of an application with respect to any drug under this

section if the Secretary finds (1) that clinical or other experience, tests, or other scientific data show that such drug is unsafe for use under the conditions of use upon the basis of which the application was approved; (2) that new evidence of clinical experience, not contained in such application or not available to the Secretary until after such application was approved, or tests by new methods, or tests by methods not deemed reasonably applicable when such application was approved, evaluated together with the evidence available to the Secretary when the application was approved, shows that such drug is not shown to be safe for use under the conditions of use upon the basis of which the application was approved; or (3) on the basis of new information before him with respect to such drug, evaluated together with the evidence available to him when the application was approved, that there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling thereof; or (4) the patent information prescribed by subsection (c) of this section was not filed within thirty days after the receipt of written notice from the Secretary specifying the failure to file such information; or (5) that the application contains any untrue statement of a material fact: *Provided*, That if the Secretary (or in his absence the officer acting as Secretary) finds that there is an imminent hazard to the public health, he may suspend the approval of such application immediately, and give the applicant prompt notice of his action and afford the applicant the opportunity for an expedited hearing under this subsection; but the authority conferred by this proviso to suspend the approval of an application

shall not be delegated. The Secretary may also, after due notice and opportunity for hearing to the applicant, withdraw the approval of an application submitted under subsection (b) or (j) of this section with respect to any drug under this section if the Secretary finds (1) that the applicant has failed to establish a system for maintaining required records, or has repeatedly or deliberately failed to maintain such records or to make required reports, in accordance with a regulation or order under subsection (k) of this section or to comply with the notice requirements of section 360(k)(2) of this title, or the applicant has refused to permit access to, or copying or verification of, such records as required by paragraph (2) of such subsection; or (2) that on the basis of new information before him, evaluated together with the evidence before him when the application was approved, the methods used in, or the facilities and controls used for, the manufacture, processing, and packing of such drug are inadequate to assure and preserve its identity, strength, quality, and purity and were not made adequate within a reasonable time after receipt of written notice from the Secretary specifying the matter complained of; or (3) that on the basis of new information before him, evaluated together with the evidence before him when the application was approved, the labeling of such drug, based on a fair evaluation of all material facts, is false or misleading in any particular and was not corrected within a reasonable time after receipt of written notice from the Secretary specifying the matter complained of. Any order under this subsection shall state the findings upon which it is based. The Secretary may withdraw the approval of an application submitted under this section, or suspend the

approval of such an application, as provided under this subsection, without first ordering the applicant to submit an assessment of the approved risk evaluation and mitigation strategy for the drug under section 355-1(g)(2)(D) of this title.

(f) Revocation of order refusing, withdrawing or suspending approval of application

Whenever the Secretary finds that the facts so require, he shall revoke any previous order under subsection (d) or (e) of this section refusing, withdrawing, or suspending approval of an application and shall approve such application or reinstate such approval, as may be appropriate.

(g) Service of orders

Orders of the Secretary issued under this section shall be served (1) in person by any officer or employee of the Department designated by the Secretary or (2) by mailing the order by registered mail or by certified mail addressed to the applicant or respondent at his last-known address in the records of the Secretary.

(h) Appeal from order

An appeal may be taken by the applicant from an order of the Secretary refusing or withdrawing approval of an application under this section. Such appeal shall be taken by filing in the United States court of appeals for the circuit wherein such applicant resides or has his principal place of business, or in the United States Court of Appeals for the District of Columbia Circuit, within sixty days after the entry of such order, a written petition praying that the order of the Secretary be set aside. A copy of such petition shall be forthwith transmitted by the clerk of

the court to the Secretary, or any officer designated by him for that purpose, and thereupon the Secretary shall certify and file in the court the record upon which the order complained of was entered, as provided in section 2112 of Title 28. Upon the filing of such petition such court shall have exclusive jurisdiction to affirm or set aside such order, except that until the filing of the record the Secretary may modify or set aside his order. No objection to the order of the Secretary shall be considered by the court unless such objection shall have been urged before the Secretary or unless there were reasonable grounds for failure so to do. The finding of the Secretary as to the facts, if supported by substantial evidence, shall be conclusive. If any person shall apply to the court for leave to adduce additional evidence, and shall show to the satisfaction of the court that such additional evidence is material and that there were reasonable grounds for failure to adduce such evidence in the proceeding before the Secretary, the court may order such additional evidence to be taken before the Secretary and to be adduced upon the hearing in such manner and upon such terms and conditions as to the court may seem proper. The Secretary may modify his findings as to the facts by reason of the additional evidence so taken, and he shall file with the court such modified findings which, if supported by substantial evidence, shall be conclusive, and his recommendation, if any, for the setting aside of the original order. The judgment of the court affirming or setting aside any such order of the Secretary shall be final, subject to review by the Supreme Court of the United States upon certiorari or certification as provided in section 1254 of Title 28. The commencement of proceedings under this subsection shall not,

unless specifically ordered by the court to the contrary, operate as a stay of the Secretary's order.

* * *

21 U.S.C. § 393. Food and Drug Administration

(a) In general

There is established in the Department of Health and Human Services the Food and Drug Administration (hereinafter in this section referred to as the "Administration").

(b) Mission

The Administration shall—

(1) promote the public health by promptly and efficiently reviewing clinical research and taking appropriate action on the marketing of regulated products in a timely manner;

(2) with respect to such products, protect the public health by ensuring that—

(A) foods are safe, wholesome, sanitary, and properly labeled;

(B) human and veterinary drugs are safe and effective;

(C) there is reasonable assurance of the safety and effectiveness of devices intended for human use;

(D) cosmetics are safe and properly labeled; and

(E) public health and safety are protected from electronic product radiation;

(3) participate through appropriate processes with representatives of other countries to reduce the burden of regulation, harmonize regulatory requirements, and achieve appropriate reciprocal arrangements; and

(4) as determined to be appropriate by the Secretary, carry out paragraphs (1) through (3) in consultation with experts in science, medicine, and public health, and in cooperation with consumers, users, manufacturers, importers, packers, distributors, and retailers of regulated products.

* * *

21 C.F.R. § 201.80. Specific requirements on content and format of labeling for human prescription drug and biological products; older drugs not described in § 201.56(b)(1).

Each section heading listed in § 201.56(d), if not omitted under § 201.56(d)(3), shall contain the following information in the following order:

* * *

(e) *Warnings.* Under this section heading, the labeling shall describe serious adverse reactions and potential safety hazards, limitations in use imposed by them, and steps that should be taken if they occur. The labeling shall be revised to include a warning as soon as there is reasonable evidence of an association of a serious hazard with a drug; a causal relationship need not have been proved. A specific warning relating to a use not provided for under the "Indications and Usage" section of the labeling may be required by the Food and Drug Administration if the drug is commonly prescribed for a disease or condition, and there is lack of substantial evidence of effectiveness for that disease or condition, and such usage is associated with serious risk or hazard. Special problems, particularly those that may lead to death or serious injury, may be required by the Food and Drug Administration to be placed in a prominently displayed box. The boxed warning ordinarily shall be based on clinical data, but serious animal toxicity may also be the basis of a boxed warning in the absence of clinical data. If a boxed warning is required, its location will be specified by the Food and Drug Administration. The frequency of these serious adverse reactions and, if known, the approxi-

mate mortality and morbidity rates for patients sustaining the reaction, which are important to safe and effective use of the drug, shall be expressed as provided under the "Adverse Reactions" section of the labeling.

* * *

21 C.F.R. § 314.70. Supplements and other changes to an approved application.

* * *

(c) *Changes requiring supplement submission at least 30 days prior to distribution of the drug product made using the change (moderate changes).* (1) A supplement must be submitted for any change in the drug substance, drug product, production process, quality controls, equipment, or facilities that has a moderate potential to have an adverse effect on the identity, strength, quality, purity, or potency of the drug product as these factors may relate to the safety or effectiveness of the drug product. If the supplement provides for a labeling change under paragraph (c)(6)(iii) of this section, 12 copies of the final printed labeling must be included.

(2) These changes include, but are not limited to:

(i) A change in the container closure system that does not affect the quality of the drug product, except those described in paragraphs (b) and (d) of this section; and

(ii) Changes solely affecting a natural protein, a recombinant DNA-derived protein/polypeptide or a complex or conjugate of a drug substance with a monoclonal antibody, including:

(A) An increase or decrease in production scale during finishing steps that involves different equipment; and

(B) Replacement of equipment with that of a different design that does not affect the process methodology or process operating parameters.

(iii) Relaxation of an acceptance criterion or deletion of a test to comply with an official compendium that is consistent with FDA statutory and regulatory requirements.

(3) A supplement submitted under paragraph (c)(1) of this section is required to give a full explanation of the basis for the change and identify the date on which the change is to be made. The supplement must be labeled "Supplement—Changes Being Effected in 30 Days" or, if applicable under paragraph (c)(6) of this section, "Supplement—Changes Being Effected."

(4) Pending approval of the supplement by FDA, except as provided in paragraph (c)(6) of this section, distribution of the drug product made using the change may begin not less than 30 days after receipt of the supplement by FDA. The information listed in paragraphs (b)(3)(i) through (b)(3)(vii) of this section must be contained in the supplement.

(5) The applicant must not distribute the drug product made using the change if within 30 days following FDA's receipt of the supplement, FDA informs the applicant that either:

(i) The change requires approval prior to distribution of the drug product in accordance with paragraph (b) of this section; or

(ii) Any of the information required under paragraph (c)(4) of this section is missing; the applicant must not distribute the drug product made using the change until the supplement has been amended to provide the missing information.

(6) The agency may designate a category of changes for the purpose of providing that, in the case of a change in such category, the holder of an approved application may commence distribution of the drug product involved upon receipt by the agency of a supplement for the change. These changes include, but are not limited to:

(i) Addition to a specification or changes in the methods or controls to provide increased assurance that the drug substance or drug product will have the characteristics of identity, strength, quality, purity, or potency that it purports or is represented to possess;

(ii) A change in the size and/or shape of a container for a nonsterile drug product, except for solid dosage forms, without a change in the labeled amount of drug product or from one container closure system to another;

(iii) Changes in the labeling, except for changes to the information required in § 201.57(a) of this chapter (which must be made pursuant to paragraph (b)(2)(v)(C) of this section), to accomplish any of the following:

(A) To add or strengthen a contraindication, warning, precaution, or adverse reaction;

(B) To add or strengthen a statement about drug abuse, dependence, psychological effect, or overdosage;

(C) To add or strengthen an instruction about dosage and administration that is intended to increase the safe use of the drug product;

(D) To delete false, misleading, or unsupported indications for use or claims for effectiveness; or

(E) Any labeling change normally requiring a supplement submission and approval prior to distribution of the drug product that FDA specifically requests be submitted under this provision.

(7) If the agency disapproves the supplemental application, it may order the manufacturer to cease distribution of the drug product(s) made with the manufacturing change.

* * *

No. 06-1249

IN THE

Supreme Court of the United States

WYETH,
Petitioner,
v.
DIANA LEVINE,
Respondent.

ON WRIT OF CERTIORARI TO
THE VERMONT SUPREME COURT

REPLY BRIEF FOR PETITIONER

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CORPORATE DISCLOSURE STATEMENT

Petitioner Wyeth has no parent corporation, and no publicly held company owns 10% or more of its stock.

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REPLY BRIEF FOR PETITIONER

Conflict preemption operates by force of the Constitution itself, and the conflict here is manifest. Fulfilling its mandate under the FDCA, FDA concluded that Phenergan was safe and effective for use under the conditions described in the approved labeling. That labeling included specific cautionary language directed to "IV push." Under the circumstances presented here, the FDCA and its implementing regulations prohibited Wyeth from changing that labeling without FDA's prior approval. But a jury applying Vermont law concluded that Wyeth was *required* to change the Phenergan labeling to contraindicate a method of administration that FDA had approved, based on a weighing of risk and benefit different from FDA's. The jury's application of Vermont law and FDA's expert administra-

tion of federal law are thus in direct conflict. None of the sources respondent invokes to divine congressional intent diminishes that conclusion.

To distract from that point, respondent claims that FDA never actually considered the risks of IV push, and that the jury's verdict therefore did not directly second-guess any judgment or command FDA actually made. That contention is both legally irrelevant and factually wrong. It is legally irrelevant because the FDCA requires FDA to consider the risks and benefits of all conditions of use, including methods of administration, presented in a New Drug Application (NDA). Respondent has not suggested that FDA was not *informed* about the risks of IV (or IV push) administration of Phenergan; to the contrary, her theory has always been that FDA simply made a wrong judgment despite having that information. FDA should be presumed, however, to have examined in good faith all information it possessed relevant to its approval decision. Requiring (or allowing) litigants to probe whether FDA focused on a precise piece of information or possible labeling variation would be unworkable and would impose a significant burden on the agency.

The contention is also factually wrong because FDA was fully aware of the harm that could result from exposure of arterial blood to Phenergan, and considered the particular risks posed by IV administration of Phenergan, including IV push. That is why FDA repeatedly directed Wyeth to include prominent warnings that IV administration required "extreme care," or "gangrene requiring amputation" would "likely" follow. These warnings, and the many instructions aimed at reducing the risk of arterial exposure, represented FDA's considered judgment of how the labeling should address the risk at issue in this case, and FDA reached

that judgment with full attention to all methods of IV administration. There is therefore no room for respondent to argue that the jury's conclusion does not contradict that of FDA.

Obscuring that patent conflict, respondent and a chorus of amici treat this case as though it were about something else—a case in which a drug manufacturer concealed risk information from FDA, or in which material information about a drug's risks emerged after FDA approved the drug and its labeling. Whatever might be said about preemption in those situations, they are most definitely not this case. Respondent never argued that Wyeth concealed information from FDA, and never contended that Wyeth should have changed its labeling to reflect information that came to light after its labeling was approved. Respondent tried *this* case on the theory that FDA had the pertinent information but reached the wrong conclusion, and that the jury should set FDA right. In this situation, state tort law is undoubtedly preempted.

ARGUMENT

I. WYETH COULD NOT COMPLY WITH BOTH STATE AND FEDERAL LABELING DUTIES

In general, federal law prohibits changes to drug labeling unless a manufacturer obtains prior FDA approval of a supplemental New Drug Application (sNDA). That prohibition is inherent in the FDCA itself: the hallmark of the Act is the requirement of prior approval by an expert agency that balances the safety and efficacy of new drugs according to the conditions of use comprehended by their labeling, and labeling is FDA's principal tool for striking that balance. Thus, FDA's final approval in 1998 of Wyeth's sNDA for Phenergan was conditioned on Wyeth's making specific

changes to the labeling, and FDA instructed Wyeth that the final printed labeling "must be identical" to the wording in the approved application. JA 382; *see also* JA 356-365. Were there any doubt concerning the FDCA's prohibition on unilateral labeling changes, FDA has resolved it by explicitly prohibiting them, with only narrow exceptions. 21 C.F.R. § 314.70(b)(2)(v)(A), (b)(3). Under that regulation, Wyeth could have changed Phenergan's labeling only through the CBE exception. That exception permitted no change in this case.

A. Federal Law Generally Prohibits Unilateral Changes To FDA-Approved Labeling

Respondent contends (Br. 21-22, 32-36) that the FDCA broadly allows manufacturers to make unilateral changes to the labeling of an approved drug without obtaining FDA approval, subject only to the statutory prohibition against distributing "misbranded" drugs. That is incorrect. The statute's text recognizes no exception to the prior-approval requirement that would permit manufacturers to distribute drugs with labeling that deviates from the FDA-approved language.[1] And the structure of the Act—independent of the prohibition on "misbranding"—is incompatible with allowing manufacturers to make unilateral labeling changes.

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[1] Notably, when Congress wished to allow manufacturers to make unilateral changes in the *manufacturing* process of an approved drug (also a component of the NDA), it expressed that intent by amending the FDCA specifically to allow such deviations from the NDA. *See* Pub. L. No. 105-115, § 116(a), 111 Stat. 2296, 2313-2315 (codified at 21 U.S.C. § 356a).

The innovation of the 1938 FDCA was to augment previously existing federal prohibitions on adulteration and misbranding with a comprehensive pre-marketing approval scheme. The FDCA as amended prohibits distribution of a new drug unless an application approved by FDA is effective with respect to that drug. 21 U.S.C. § 355(a); *see also id.* § 331(d). The labeling to be used for the drug is a central component of that application, *id.* § 355(b)(1)(F), and must be approved before the application becomes effective, *id.* § 355(d)(7). FDA's review of the safety and efficacy of the drug focuses on "the conditions prescribed, recommended, or suggested in the proposed labeling." *Id.* § 355(d)(1), (2), (4), (5). Approved labeling is therefore inseparable from FDA's approval of the drug itself. *See* 71 Fed. Reg. 3922, 3934 (Jan. 24, 2006). As this Court held in the analogous context of pre-marketing approval of medical devices, where FDA's safety and effectiveness determination is based on the terms of the application as approved, it follows that the approved product must be marketed "with almost no deviations from the specifications in [that] application." *Riegel* v. *Medtronic, Inc.*, 128 S. Ct. 999, 1007 (2008).

Respondent concedes (Br. 35-36) that at least some labeling changes could render the drug a "new drug" for which no approved application is effective and would therefore be prohibited by the statute. Respondent nevertheless argues that labeling changes intended to add or strengthen warnings or (as here) to withdraw uses or methods of administration would not result in a new drug and may therefore be made unilaterally, subject only to the statutory prohibition against misbranding. That too is incorrect. "[S]ubstantive changes in labeling ... are more likely than other changes to affect the agency's previous conclusions

about the safety and effectiveness of the drug." 50 Fed. Reg. 7452, 7470 (Feb. 22, 1985). For that reason, FDA has provided that many kinds of labeling changes—including changes to methods of administration—may render a drug a "new drug" requiring new approval. 21 C.F.R. § 310.3(h)(5).[2]

Under respondent's contrary view, Wyeth could have changed Phenergan's labeling to contraindicate any form of administration it wished without seeking FDA's approval. Her theory would extend even to unilateral contraindication of *intramuscular* injection, even though doing so would directly contradict FDA's judgment that deep IM injection is the preferred route of administration, JA 391, and would affect the safety of the drug by leaving no option other than the IV route. FDA was required to make, and did make, a determination about the balance between safety and efficacy with respect to *all* approved methods of administration. Any change unilaterally contraindicating one of those methods can undermine the balance Congress intended FDA to strike. That is why federal law with only limited exceptions precludes manufacturers from making such changes without FDA approval.[3]

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[2] Respondent reasons (Br. 37) that because Wyeth could have withdrawn Phenergan from the market altogether, it must have had the lesser power to withdraw a method of administration from Phenergan's labeling. That ignores the nature of a licensing regime: a licensee may choose not to exercise its license at all, but it cannot exercise that license without regard to its terms and conditions.

[3] Citing extra-record material, respondent's amici assert that manufacturers frequently make unilateral changes to drug labeling without FDA taking any enforcement action. But as FDA has explained, in practice manufacturers routinely consult with FDA

To the extent the FDCA leaves room for manufacturers to make any unilateral labeling changes, FDA long ago made clear that as a general rule, labeling changes may be made only with FDA's prior approval. 21 C.F.R. § 314.70(b)(1), (b)(2)(v)(A), (b)(3). The only exceptions are minor or editorial changes that do not affect drug safety or efficacy, *id.* § 314.70(d)(2)(ix), (x), and CBE changes that require FDA approval but may be implemented upon submission of a supplemental application, *id.* § 314.70(c)(6)(iii). Respondent does not claim these regulations rest on an unreasonable reading of the FDCA or are otherwise invalid. Wyeth could therefore have changed the Phenergan labeling after FDA approved its sNDA in 1998 only if a change would have been permissible under the CBE exception. It would not have been.

B. The CBE Exception Did Not Permit Wyeth To Eliminate IV Push From Phenergan's Labeling

The CBE exception allows manufacturers to make labeling changes before FDA acts on an sNDA only

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before changing risk information on labeling. 71 Fed. Reg. at 3934; 73 Fed. Reg. 2848, 2849 (Jan. 16, 2008). Since manufacturers rarely act unilaterally in implementing labeling changes, it is no surprise FDA rarely has to take enforcement action against them for doing so.

Moreover, the cited examples cannot be taken at face value. One brief, for example, contends that Wyeth unilaterally added a warning to the labeling of its drug Effexor, based on no new information and with no negative enforcement consequences from FDA. *See* Witczak Amicus Br. 5-8. That is wrong. Wyeth submitted the proposed warning to FDA in a CBE supplement, citing new developments in the industry's understanding of risks associated with drugs like Effexor. FDA considered the change and rejected it, instructing Wyeth to use a different warning.

when necessary "to correct concerns about newly discovered risks from the use of the drug." 47 Fed. Reg. 46,622, 46,623 (Oct. 19, 1982); *see also* U.S. Br. 22-23 (June 2, 2008). As demonstrated in Wyeth's opening brief (at 35-39), the CBE regulation reflects FDA's discretionary decision to forbear from taking enforcement action against distribution of a drug with labeling that differs from that approved in the NDA.

FDA introduced the CBE exception in 1965 as an incremental change to a regime that otherwise permitted no labeling changes at all without prior approval, *see* Pet. Br. 35-37, so that new information or conclusions about drug safety could be "placed into effect at the earliest possible time." 30 Fed. Reg. 993, 993 (Jan. 30, 1965). Refinements in 1982 retained the prior-approval requirement for all labeling changes except minor editorial revisions and changes made "to correct concerns about newly discovered risks from the use of the drug" and to "make available important new information about the safe use of a drug product." 47 Fed. Reg. at 46,623, 46,635. And FDA recently amended the CBE again to codify its "longstanding view" that CBE changes are appropriate "only to reflect newly acquired information," and "only if there is sufficient evidence of a causal association" between the drug and the risk at issue. 73 Fed. Reg. 49,603, 49,603, 49,604 (Aug. 22, 2008); *see also id.* at 49,608 (amendment did not effect a "substantive policy change" or "alter the agency's current practices").

FDA's interpretation of its own regulation is entitled to deference, *see Auer* v. *Robbins*, 519 U.S. 452, 461 (1997), particularly here, where the regulation reflects FDA's exercise of its substantial discretion to enforce the statute, *see* 30 Fed. Reg. at 994; *see also Heckler* v. *Chaney*, 470 U.S. 821, 835 (1985). As FDA has

explained, the CBE exception must be construed narrowly because FDA's "comprehensive scientific evaluation of the product's risks and benefits ... is embodied in the labeling for the product[.]" 73 Fed. Reg. at 49,604.

Respondent (Br. 8) cites another FDA regulation requiring manufacturers to revise drug labeling "as soon as there is reasonable evidence of an association of a serious hazard with a drug." 21 C.F.R. § 201.80(e). That regulation does not support a broader reading of the CBE exception. Nothing in section 201.80(e) suggests that the required revisions should be made without FDA's approval. Section 201.80(e) states a substantive standard for labeling changes; it does not create an alternative procedure for making them. And because section 201.80(e) requires labeling changes "as soon as" evidence of a hazard emerges, that regulation too is directed to new safety information. Reading section 201.80(e) to require unilateral labeling changes would render the CBE exception a nullity—for in respondent's view, the CBE exception would simply permit what section 201.80(e) already required.[4]

Under the proper construction of the CBE exception, Wyeth had no good-faith basis to implement a CBE change. Respondent never alleged that Wyeth

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[4] Respondent (Br. 8 n.5) cites *Werner v. Upjohn Co.*, 628 F.2d 848 (4th Cir. 1980), for the claim that FDA's regulations encourage unilateral action by manufacturers to improve warnings, but that court did not address whether such changes would be appropriate when the change did not reflect new safety information. To the contrary, the court explained that FDA regulations allow labeling changes without prior approval "where new side effects are discovered by the company." *Id.* at 859.

had information about the risks of Phenergan it did not disclose to FDA. Rather, respondent's theory of liability has been that Phenergan's labeling failed to foreclose a method of administration that carried a risk of which Wyeth and FDA were both aware when FDA approved that labeling. *See infra* pp. 16-18. And while FDA's recent regulation provides that "newly acquired information" can include new analyses of old information previously submitted to FDA, so long as it reveals a risk of a "different type or greater severity or frequency than previously included in submissions to FDA," 73 Fed. Reg. at 49,604, respondent did not claim that any such new analysis came to light between FDA's approval of Phenergan's labeling in 1998 and respondent's injury in 2000.[5] Because no CBE change was permissible, federal law prohibited Wyeth from changing the Phenergan labeling that FDA instructed it to use.[6]

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[5] Respondent's amicus, while claiming that "analyses might have revealed the extent of the dangers posed by Phenergan"—apparently referring to the very dangers the labeling already warned of—rests that contention on extra-record studies and reports published years after respondent's treatment with Phenergan. *See* Budhwani Amicus Br. 18; *see also id.* at 15-23. The brief suggests no reason why Wyeth should have reached a different conclusion in 2000 about Phenergan's risks than FDA had reached when it approved the labeling in 1998.

[6] Respondent questions (Br. 18-19, 43 n.29) whether Wyeth adequately raised below its argument that the CBE regulation permits only labeling changes based on new safety information. But Wyeth advanced that construction before the Vermont Supreme Court, *see* Wyeth Br. 13-14, 24 (Vt. Nov. 22, 2004), which rejected it, *see* Pet. App. 11a, 13a. Moreover, interpretation of the CBE exception—and the question of preemption—are questions of law, so there was no reason to argue them to the jury or to object

C. Respondent's Remaining Arguments Fail To Show That Wyeth Could Comply With Both State And Federal Law

Respondent contends (Br. 43-45) that Wyeth could have complied with both federal and state law simply by paying respondent's money judgment, without changing Phenergan's labeling. But this Court has made clear that "common-law liability is premised on the existence of a legal duty, and a tort judgment therefore establishes that the defendant has violated a state-law obligation." *Riegel*, 128 S. Ct. at 1008 (quotation marks omitted); *see also Medtronic, Inc.* v. *Lohr*, 518 U.S. 470, 504 (1996) (Breyer, J., concurring in part and concurring in the judgment). State tort law is therefore subject to preemption every bit as much as positive enactments of state law. *See, e.g., Bates* v. *Dow Agrosciences LLC*, 544 U.S. 431, 443 (2005); *Geier* v. *American Honda Motor Co.*, 529 U.S. 861, 881 (2000). That conclusion certainly applies to "impossibility" conflict preemption, which asks whether "compliance" with both state and federal law is impossible. *E.g., Fidelity Fed. Sav. & Loan Ass'n* v. *de la Cuesta*, 458 U.S. 141, 153 (1982). As the Court has held, state law is preempted where it is "impossible to comply with [federal] regulation *without incurring liability* under state common law." *Sprietsma* v. *Mercury Marine*, 537 U.S. 51, 65 (2002) (emphasis added).

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to particular jury instructions. And in light of respondent's own contention at trial that Wyeth and FDA were fully aware of the relevant risks, *see infra* pp. 17-18, no remand is required to assess whether the evidence would have supported a labeling change under the CBE exception as interpreted by FDA (*cf.* Resp. Br. 43 n.29).

Respondent alternatively contends (Br. 37) that Wyeth could have filed a supplemental application proposing to contraindicate IV push and implemented the change upon FDA approval. But there is no reason to assume FDA would have approved a hypothetical proposed change, and it is unworkable for that counterfactual inquiry to be the touchstone of the preemption analysis. FDA does not approve all proposed labeling changes. *See, e.g.*, JA 271, 359; *see also Colacicco* v. *Apotex Inc.*, 521 F.3d 253, 269-271 (3d Cir. 2008); *Dowhal* v. *Smithkline Beecham Consumer Healthcare*, 88 P.3d 1, 4-6 (Cal. 2004). Respondent's theory would inappropriately assign to juries the speculative task of determining whether and when FDA would have approved a particular hypothetical labeling change. This Court has disapproved similar undertakings. *See Arkansas La. Gas Co.* v. *Hall*, 453 U.S. 571, 578-579, 580-581 (1981); *Buckman Co.* v. *Plaintiffs' Legal Comm.*, 531 U.S. 341, 354 (2001) (Stevens, J., concurring in the judgment). And in any event, on the record here, Wyeth had no new information unknown to FDA that could have been the basis of a supplemental NDA.[7]

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[7] Moreover, respondent offers no reason to believe that merely submitting a proposed change to FDA would discharge Wyeth's purported state-law duty. As respondent herself has explained, "the state-law duty imposed ... here is premised on the label's failure to have proper warnings or instructions regarding IV-push administration," Resp. Br. 52 n.37 (emphasis omitted), not on any failure to propose that change. The suggestion advanced by some of respondent's amici that Wyeth could have issued a "Dear Doctor" letter is similarly irrelevant; respondent's theory of liability was premised on "the *label's* failure to have proper warnings or instructions." *Id.* (emphasis added); *see also* JA 17 (¶ 17).

II. Enforcement Of The State-Law Duty Invoked By Respondent Would Obstruct The Purposes Of The FDCA And FDA's Regulations

Congress intended that drug-labeling approval decisions be made by an agency that makes expert scientific judgments, balancing safety and efficacy to benefit overall public health. In approving Wyeth's sNDA in 1998, FDA concluded that the benefits of Phenergan outweighed its risks under all conditions of use comprehended by the labeling, including administration by IV push. Yet under state law, a jury was permitted to decide that the same drug was *not* safe and effective under the approved labeling. By directly contradicting FDA's judgment, the jury's enforcement of state law conflicted with and frustrated the objectives of federal law.[8]

Respondent attempts to evade this conflict by asserting, first, that FDA made no judgment balancing the risks and benefits of IV push, so that the jury's verdict did not contradict FDA's approval of Phenergan's labeling. Respondent further argues that Congress did not intend to preempt common-law remedies, which are said to complement FDA regulation and serve the same objectives. These arguments fail.

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[8] Respondent has wisely abandoned the Vermont Supreme Court's reasoning that section 202 of the 1962 Drug Amendments precludes application of "obstacle" preemption to cases under the FDCA. Resp. Br. 54 n.40.

A. The Jury Directly Contradicted FDA's Judgment About What Phenergan's Labeling Should Say About IV Administration (Including IV Push)

At trial, respondent's counsel expressly exhorted the jury to override FDA's judgment: "The FDA doesn't make the decision, you do." JA 212. In this Court, respondent contends (*e.g.*, Br. 1, 16, 47-48) that no rational person could find—as FDA did—that the benefits of IV push ever outweigh its risks.[9] Those arguments underscore what respondent's suit is really about: second-guessing FDA's judgment about the relative risks and benefits of IV administration and how those risks should be managed and communicated by the drug's labeling. The Phenergan labeling in place when respondent was injured was the language FDA approved and directed Wyeth to use. FDA made that approval decision based on the information available about the risks of IV administration, including IV-push injection. The state-law duty respondent seeks to enforce was a duty to use different labeling based on the

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[9] Both the physician assistant and the attending physician testified that IV-push injection was appropriate because earlier intramuscular injection had been ineffective, and faster delivery of a higher concentration was needed because Phenergan was being given in combination with IV-push Demerol. JA 40-41, 60-61, 104-106. (Respondent never argued Demerol should not have been given by push.) While the evidence was mixed whether IV drip is as risk-free as respondent suggests, *see* JA 67, 75, it is clear that drip delivers lower concentrations at slower rates, and therefore would not have achieved the benefits respondent needed and IV push offered (when performed correctly). *See, e.g.*, JA 187. The PA thus explained that she chose push over drip because she needed to treat respondent "in a swift and timely way," JA 106, 109, and that she had done so effectively for years, JA 104-105; Tr. 69 (Mar. 12, 2004). *See also* Pet. Br. 19 n.10, 22 n.11.

view that FDA got it wrong—a clear conflict between state and federal law.

Respondent seeks to avoid that conclusion by arguing that in this case, the jury and FDA did not reach judgments about the same thing. Whereas the jury found Phenergan's labeling to be inadequate specifically with respect to IV push, respondent contends, FDA considered only IV administration generally and made no determination regarding IV push. That contention does not withstand scrutiny.

First, FDA was required by statute to evaluate Phenergan's safety and efficacy under all conditions of use comprehended by the labeling and to find the labeling adequate to permit safe use before approving the drug. 21 U.S.C. § 355(d). The labeled conditions of use directly addressed IV administration, including by IV push. Consistent with its statutory mandate, FDA must therefore be presumed to have made a judgment about the risks and benefits of IV push before approving Phenergan for distribution with that labeling. *Cf. United States* v. *Chemical Found., Inc.*, 272 U.S. 1, 14-15 (1926) ("The presumption of regularity supports the official acts of public officers, and, in the absence of clear evidence to the contrary, courts presume that they have properly discharged their official duties.").

Second, whether or not the jury's verdict actually reflected a judgment about IV push, rather than IV generally—a matter on which the record is unclear[10]—

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[10] Respondent's primary claim at trial was that the Phenergan labeling should have contraindicated all IV administration; warning against IV push was a second-best alternative advanced by some of her witnesses. JA 31-32, 36, 59, 63, 65, 79-81, 83, 211. Neither the jury instructions nor the verdict form required the

it is entirely clear that FDA made a judgment about IV push. Several of the instructions for IV administration on the labeling that FDA reviewed and approved are applicable *only* to injection by IV push.[11] Furthermore, the record of meetings and correspondence between Wyeth and FDA regarding Phenergan's labeling shows FDA considered IV push.[12] FDA's 1987 letter to Wyeth cited twenty medical journal articles it had reviewed that discuss intra-arterial injection. JA 313-315.

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jury to make any finding specific to IV push. JA 220, 225-226. Whichever theory the jury accepted contradicted FDA's judgment. That respondent was permitted to present both arguments underscores the broad scope of the conflict.

[11] JA 390-391. Respondent's physician explained at trial that the labeling's recommended rate of administration (not to exceed 25 mg per minute) refers to "IV push, as opposed to say being in a bag and dripped over a couple of hours." JA 52. The labeling's reference to "plungers" and "rigid needles" likewise suggests injection by IV push: "by talking plungers and rigid needles, that's the way you do it, to push it with the plunger." JA 53. He further explained that aspiration, which is also discussed in the labeling, is a step in the process of IV push. JA 47-48. The labeling also gives instructions for use of the Tubex Injector—a single-use cartridge and reusable plastic injector with a rigid plunger used to administer a single dose of Phenergan by IV push injection. JA 107, 391.

[12] For example, at the 1976 Advisory Committee meeting addressing proposed revisions to the labeling, a question arose regarding the difficulty of aspiration and detection of arterial pressure using the Tubex Injector instead of a "plain needle and syringe." JA 294. These references to aspiration, use of the Tubex, and use of a needle and syringe relate only to IV push. Similarly, in a 1987 letter to Wyeth, FDA suggested enhanced safety could be achieved using a "running intravenous" system. JA 312. (A "running IV" is the same thing as "IV drip." JA 15-16.) FDA thus considered not only the risks associated with IV push, but also the possibility that IV drip might provide a safer alternative.

Those articles confirm that the danger FDA was concerned about was caused by IV push.[13] FDA was thus focused on a risk associated specifically with IV push and was aware of the differences between IV push and IV drip.[14] Indeed, if, as respondent contends (Br. 1), IV drip poses "virtually no risk," then the risks and adverse events FDA considered and addressed on the labeling could *only* have concerned IV push.

Consistent with this record, respondent's witnesses testified that FDA knew the risks of IV administration of Phenergan, including IV push. One of respondent's experts testified that "FDA knew about the risks" that were the subject of respondent's claims, had discussed those risks in correspondence with Wyeth, and had received relevant adverse event reports. JA 97. Another of respondent's experts agreed that the reports FDA received discussed cases where Phenergan caused amputation as a result of "direct injection ... not any other

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[13] Several articles reported on cases in which patients suffered serious injury, including gangrene requiring amputation, as a result of IV injections of Phenergan or other drugs administered by IV push. *See, e.g.*, Webb & Lampert, *Accidental Arterial Injections*, 101 Am. J. Obst. & Gynec. 365, 366 (1968); Hager & Wilson, *Gangrene of the Hand Following Intra-Arterial Injection*, 94 Arch. Surg. 86, 86 (1967); Miller et al., *Intra-Arterial Injection of a Barbiturate—A Case Report*, 23 Anesthesia Progress 25, 26 (1976). One cited article even discussed the relative safety of IV drip compared to IV push but noted that IV drip may sometimes be impractical. Webb & Lampert, at 371.

[14] No court below found that FDA was unaware of the risks of IV push or the differences between push and drip. The statements cited by respondent (Br. 19-20, 51-52) speak only to the supposed lack of evidence showing why FDA rejected the labeling change Wyeth proposed in 1988 or whether FDA would have rejected all such warnings.

method of injection." JA 74; *see also* Tr. 222-225 (Mar. 8, 2004) (testifying about FDA's awareness of several cases of injury caused by direct IV injection).

Respondent (Br. 53 & n.38) analogizes this case to *Sprietsma* and *Lohr*, but it actually mirrors *Geier*, where the agency made a specific judgment that balanced competing considerations to promote its ultimate safety objective. In that situation, this Court concluded that a state-law tort duty that would have upset that regulatory balance could not stand. *See* 529 U.S. at 864-865, 874-881. In *Sprietsma*, by contrast, the Coast Guard had no statutory duty to regulate propeller guards, and accordingly made no decision regarding their desirability; thus, a tort suit enforcing a state-law judgment that propeller guards were necessary interfered with no federal judgments or objectives. *See* 537 U.S. at 61-62, 65-68. Likewise, as this Court explained in *Riegel*, the "substantial equivalence" review at issue in *Lohr* did not require FDA to conduct (and FDA did not conduct) any safety and efficacy review of the medical device at issue, and the regulatory scheme imposed no product-specific requirements. *See Riegel*, 128 S. Ct. at 1006-1007. In contrast, FDA pre-approval of drugs—like its review of the medical devices at issue in *Riegel*—is a rigorous, individualized process under which FDA approves every new drug, and Congress permits the distribution of those drugs solely under the terms of the approved application. *Id.* at 1004-1005, 1007.

Allowing a lay jury to countermand FDA's expert determination about how drug labeling should communicate a drug's risks and benefits frustrates the statu-

tory and regulatory scheme.[15] Respondent contends (Br. 51) that no conflict exists because when it comes to labeling, FDA does not balance risks and benefits. But FDA is bound by statute to balance a drug's safety and efficacy, and drug labeling is integral to that balance. 21 U.S.C. § 355(d). A drug FDA views as sufficiently beneficial to warrant approval despite its risks under certain labeled conditions might not provide the same net benefit if the conditions of use on the labeling were altered. FDA's judgment that the labeling it approves strikes the best balance in light of the information it has reviewed and is the *correct* standard—not a *minimum* standard—is entitled to significant weight, for FDA is best positioned to assess whether and how conflicting state labeling requirements would affect drug

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[15] That conflict would exist even if respondent were correct that the CBE regulation would have permitted Wyeth to implement a unilateral labeling change without any new information about the risks of IV push. It would be one thing for federal law (as respondent would read it) to allow a manufacturer to make an interim labeling change while asking FDA to reconsider its own previous judgment through an sNDA; it would be quite another for a state jury to compel a manufacturer to make a change based on the State's entirely separate, and conflicting, judgment about the propriety of the labeling. The FDCA is concerned not just with the content of drug labeling, but also with who shall make those labeling decisions. A state regime that *required* a manufacturer to implement a labeling change that federal law would merely permit it to implement temporarily while awaiting FDA's reconsideration would undermine FDA's approval authority and clash with the FDCA regulatory regime. The Court reached a similar conclusion in *Geier*: in that case, nothing in federal law prohibited manufacturers from installing airbags, yet a state law *requiring* the use of airbags still conflicted with federal law. *See* 529 U.S. at 878-879, 881; *see also de la Cuesta*, 458 U.S. at 155.

safety and efficacy. *See* 71 Fed. Reg. at 3934-3935; *see also Geier*, 529 U.S. at 883; *Lohr*, 518 U.S. at 496.[16]

B. Respondent's Arguments About Congressional Intent Fail

Respondent argues that Congress could not have intended to preempt common-law liability because the FDCA contains no express preemption clause; Congress was presumably aware of common-law tort suits involving drugs; and the FDCA and state-law duties serve the same purpose of protecting consumers. These arguments all fail.

First, although respondent invokes congressional intent, she misapprehends the intent that is pertinent here. Wyeth does not argue that Congress intended to occupy the field of pharmaceutical safety; nor does it contend that Congress intended to preempt all common-law liability for unsafe drugs. Indeed, conflict preemption does not depend on any showing that Congress ever focused on the question of common-law liability. Rather, the relevant intent is Congress's judgment that drug-labeling decisions should be made

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[16] FDA also balances competing interests to prevent manufacturers from including excessive or unsubstantiated information on labeling. 71 Fed. Reg. at 3922, 3935. Several of respondent's amici contend that the prospect of "overwarning" is illusory because it rarely occurs. But that is precisely the point. FDA oversight prevents overwarning; if manufacturers had unlimited discretion to make labeling changes without approval and could face tort liability for failing to do so, the risk of overwarning—and of deterring beneficial uses of drugs—would increase. Overwarning would also make it harder for health-care providers to locate important information on the labeling and to be confident that all information on the labeling is based on scientific evidence.

by an expert agency that balances risks and benefits and that FDA's labeling judgments should be binding on drug manufacturers. Any state-law duty that interferes with the accomplishment of those objectives is preempted under standard preemption doctrine.

The absence of an express preemption clause in the FDCA is neither dispositive nor even particularly revealing. Conflict preemption arises directly from the Supremacy Clause: where state and federal law cannot be reconciled, the Constitution requires that the state law give way. For this reason, the Court has repeatedly held that neither the absence of express preemption language nor the inclusion of express language with a limited preemptive scope forecloses preemption that arises from an actual conflict between federal and state law. *See, e.g., Freightliner Corp.* v. *Myrick*, 514 U.S. 280, 287-289 (1995); *see also Geier*, 529 U.S. at 869, 884.

The express clause in the MDA, on which respondent and her amici rely, serves a different purpose than the implied preemption rule that governs here. The MDA clause expressly preempts state-law requirements that are "different from, or *in addition to*" federal requirements. 21 U.S.C. § 360k(a) (emphasis added). The clause thus preempts non-parallel state-law requirements without any showing of actual conflict. *See Riegel*, 128 S. Ct. at 1011; *see also Bates*, 544 U.S. at 447-448, 452-454 (applying similar language). Comparing the FDCA and MDA is of limited help also because express preemption clauses are largely a modern phenomenon. *See* Zimmerman, *Preemption in the U.S. Federal System*, 23 Publius: J. Federalism 1, 1-2, 4, 6 (1993). Express preemption clauses were rare when Congress passed the FDCA in 1938, but had become much more common by the time Congress adopted the

MDA in 1976. *Id.* at 1-2. Moreover, the proliferation of state regulation of medical devices created a need for a broader preemptive scope in the MDA. *See Riegel*, 128 S. Ct. at 1003. No comparable pattern of state regulation of drugs had emerged when Congress enacted the FDCA in 1938.

Respondent and her amici invoke the history of common-law liability for failure to warn, but most of the cases they cite would not be affected by a finding of preemption here. Several of the cases involve liability for selling drugs that were adulterated or incorrectly identified and would thus have violated the FDCA. *See, e.g., Thomas* v. *Winchester*, 6 N.Y. 397 (1852); *Fisher* v. *Golladay*, 38 Mo. App. 531 (1889); *Moehlenbrock* v. *Parke, Davis & Co.*, 169 N.W. 541 (Minn. 1918). Others involved drug labeling that failed to reflect emerging risk information the manufacturer learned of but failed to disclose. *See, e.g., Bine* v. *Sterling Drug, Inc.*, 422 S.W.2d 623 (Mo. 1968); *McEwen* v. *Ortho Pharm. Corp.*, 528 P.2d 522 (Or. 1974); *Roginsky* v. *Richardson-Merrell, Inc.*, 378 F.2d 832 (2d Cir. 1967). Unlike here, the defendants in many of these cases were held liable for conduct that had not been approved by FDA or that otherwise violated federal law (which requires manufacturers promptly to disclose new safety information to FDA, *see* 21 U.S.C. § 355(k); 21 C.F.R. § 314.80). To be sure, under the principles articulated here, preemption might result in some of the cases respondent and her amici cite; but in most of those cases, a finding of preemption would have to be premised on a theory different from the one Wyeth has put forward.

The legislative history cited by respondent establishes nothing useful about congressional intent in this case. Respondent notes (Br. 4) the absence of a private

right of action in the 1938 Act that had been included in a 1933 precursor to the FDCA. But the 1933 bill would have provided a right of action for damages "caused by a violation of this Act." H.R. 6110, 73d Cong. § 25 (1933). That provision thus envisioned that *federal* law would set the relevant standard of conduct. It says nothing about Congress's intent to preserve tort suits against conduct that, like Wyeth's conduct here, does not violate the FDCA. Moreover, the 1933 version of the bill did not include the pre-approval system that was ultimately adopted in 1938. The conclusion of certain legislators that no private right of action was required in the 1933 bill therefore sheds no light on Congress's preemptive intent with respect to drug labeling that has undergone the pre-market approval process.

Respondent also cites (Br. 28-29) legislative measures from 1995 and 1997 that referred to drug manufacturer "liability" under state law. But Wyeth does not contend that the FDCA and FDA's regulations preempt all tort liability against drug manufacturers. It is therefore not significant that Congress has occasionally indicated that some tort liability would continue to coexist with federal regulation. Respondent also cites 2007 legislation that enhanced FDA's authority to order post-approval labeling changes, but preserved manufacturers' responsibility "'to maintain ... label[s] in accordance with existing requirements, including [the CBE regulation].'" Resp. Br. 38 (quoting 121 Stat. 925-926). That language preserved only requirements under federal law, and it is silent on what Congress believed those "existing requirements" entail. The language is therefore neutral on the meaning of the CBE exception and on the preemption question before the Court. *See* U.S. Br. 32-33.

Citing *Bates* and *Lohr*, respondent finally contends (Br. 45-46) that no conflict exists because both the FDCA and the Vermont-law duty to warn serve the same purpose: to protect consumers and safeguard public health. But safety is not the FDCA's sole objective. All drugs are unsafe in at least some circumstances, particularly when they might be administered incorrectly. The FDCA requires FDA to strike a balance between safety and efficacy by identifying and managing acceptable levels of risk with respect to particular drugs while also promoting availability of beneficial drugs.

By contrast, *Bates* involved a regulatory scheme in which EPA had waived all efficacy review and made no individualized determination about the labeling statements that the plaintiff's suit challenged. 544 U.S. at 440. EPA was not required, therefore, to balance consumer protection and the public health more generally in the manner that FDA must under the FDCA. Likewise, in *Lohr*, "substantial equivalence" review under the MDA required no particularized balancing of safety and effectiveness. 518 U.S. at 478-479, 493-494. Moreover, it was not the common purposes underlying state and federal law that led the Court to see no preemption in *Bates* and *Lohr*, but rather that the specific state-law duties at issue were parallel to the duties imposed by federal law. *See Bates*, 544 U.S. at 444-452; *Lohr*, 518 U.S. at 493-494, 495, 501. (Indeed, in *Bates*, the Court held that state-law labeling requirements that were not equivalent to federal requirements *would* be preempted. 544 U.S. at 452-454.) Where, as here, federal and state law impose conflicting duties, no consonance of purpose—even if it existed—could eliminate that conflict and preclude operation of the Supremacy Clause. *See Crosby* v. *National Foreign Trade Coun-*

cil, 530 U.S. 363, 379 (2000); *International Paper Co.* v. *Ouellette*, 479 U.S. 481, 494 (1987).[17]

III. The Court Should Decide This Case—Not The Other Scenarios Respondent And Her Amici Advance

Respondent's amici devote great energy to arguing that state-law tort suits should not be preempted because FDA lacks sufficient resources to monitor the safety of drugs after they (and their labeling) have been approved. Whether or not that criticism of FDA is correct—and many of amici's arguments cannot be taken at face value[18]—it is irrelevant in this case. Respondent never argued that Wyeth violated its state-law duty by concealing information from FDA or failing to change the Phenergan labeling to reflect safety information that came to its attention *after* FDA approved the labeling that was in effect when respondent was injured. Rather, respondent argued that FDA had information about the risk to which she was exposed but nonetheless made a regulatory decision that, in her

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[17] Vermont's regulatory compliance defense does not resolve the conflict. While the FDCA makes FDA approval conclusive, 21 U.S.C. § 355(a), the regulatory compliance defense does not: FDA's judgment is just one opinion the jury is free to accept or reject. *See, e.g.*, JA 216. That is not parallel to federal law.

[18] Amici's arguments rest largely on extra-record material that does not tell the whole story. For example, the brief of certain editors and authors of the *New England Journal of Medicine* (at 13-18) distorts the facts surrounding the marketing and withdrawal of Wyeth's diet drugs Pondimin and Redux. While a rejoinder to such attacks is well beyond the scope of this case and the record, their account of Wyeth's conduct in connection with those drugs is quite incorrect.

view, did not adequately protect the public from that risk.

The criticism (*e.g.*, Resp. Br. 11) that prior to 2007 FDA lacked authority to initiate labeling changes after a drug was approved is similarly irrelevant here. Whatever the limits on FDA's ability to demand labeling changes on its own initiative after it has approved a drug application, FDA certainly has authority to compel labeling changes when reviewing an NDA or sNDA by withholding approval until its demands are met. 21 U.S.C. § 355(d); 21 C.F.R. §§ 314.105(b), 314.110. That is all this case is about, and FDA exercised that authority in reviewing and approving several supplemental NDAs for Phenergan after its initial approval in 1955.[19] Indeed, FDA conditioned its 1998 approval of the Phenergan labeling in place when respondent was injured on Wyeth's implementing specific changes and distributing the drug with labeling "identical" to the FDA-approved language. JA 382; *see also* JA 356-365.

A preemption holding here will not necessarily resolve a tort suit where a manufacturer withheld safety information from FDA or learned of new safety information after FDA approved the drug's labeling. Indeed, the concern raised by these arguments is pre-

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[19] Respondent is incorrect to suggest that Wyeth disregarded FDA's labeling requests. Wyeth added all the labeling information FDA directed it to add concerning the risk of intra-arterial injection. *Compare* JA 282, 283, 285 *with* JA 351-352. In the only instance respondent cites (Br. 11) in which Wyeth allegedly did not follow FDA's instructions—which did not concern arterial exposure—Wyeth's initial disagreement was referred to an outside advisory committee, which reviewed the issue and concluded that a warning should indeed be added. JA 290-291. Wyeth added that warning. *Compare* JA 291 *with* JA 324.

cisely the concern that is addressed by FDA's interpretation of the CBE regulation and its recent revision. If a manufacturer learns of new information or draws a new conclusion about a drug's safety after FDA approval and fails to disclose that information to FDA or to reflect it in an appropriate labeling change when permitted to do so under the CBE rule, that manufacturer might not have a preemption defense to tort liability. Preemption in the circumstances of this case thus provides an incentive for manufacturers to bring new information to FDA's attention and update the labeling as soon as it comes to light.

In short, respondent and her amici are quite wrong to suggest that preemption in this case would displace all common-law remedies for injured patients. Common-law remedies may remain, for example, for injuries caused by violations of federal law. But the Supremacy Clause requires that the substantive standard of conduct that is enforced by a tort remedy be consistent with federal law. No matter its purposes or benefits, tort law cannot be said to complement federal regulation when it imposes a state-law duty that contradicts manufacturers' federal obligations and FDA's labeling approval judgments. Where those circumstances do not exist, there might be no conflict between state and federal law, and a tort remedy might be available. But where, as here, a state tort judgment would frustrate Congress's intent by challenging FDA's labeling approval judgment, that state judgment cannot stand under the Supremacy Clause.

CONCLUSION

The judgment of the Vermont Supreme Court should be reversed.

Respectfully submitted.

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IN THE

Supreme Court of the United States

WYETH,

Petitioner,

v.

DIANA LEVINE,

Respondent.

ON PETITION FOR A WRIT OF CERTIORARI
TO THE SUPREME COURT OF THE STATE OF VERMONT

SUPPLEMENTAL BRIEF FOR PETITIONER

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STATEMENT PURSUANT TO RULE 29.6

Petitioner's corporate disclosure statement was set forth at page *ii* of its Petition for a Writ of Certiorari, and there are no amendments to that statement.

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Wyeth filed a petition for writ of certiorari in the above-captioned case on March 12, 2007. *See* Petition for a Writ of Certiorari, *Wyeth v. Levine*, No. 06-1249 (U.S. Mar. 12, 2007) ("Pet."). On May 21, 2007, the Court requested the views of the United States. The United States responded on December 21, 2007 and agreed with Petitioner that Respondent's state-law claims are preempted by the Federal Food, Drug, and Cosmetic Act ("FDCA") "because they challenge labeling that FDA approved, after being informed of the relevant health risk, based on its expert weighing of the risks and benefits of requiring additional or different warnings." Brief for the United States as Amicus Curiae at 7, *Wyeth v. Levine*, No. 06-1249 (U.S. Dec. 21, 2007) ("U.S. Br."). The United States also asked the Court to hold the petition pending disposition of *Riegel v. Medtronic, Inc.*, No. 06-179 (argued Dec. 4, 2007), and *Warner-Lambert Co., LLC v. Kent*, No. 06-1498, (cert. granted Sept. 25, 2007). Petitioner respectfully submits this supplemental brief to urge the Court to grant the petition and schedule the case for review this Term.

1. The United States expressed complete agreement with two critical legal arguments set forth in the petition. Specifically, the United States agreed with Petitioner that 21 C.F.R. § 314.70, FDA's "Changes Being Effected," or "CBE" regulation, does not allow drug manufacturers unilaterally to change FDA-approved labeling to strengthen a warning unless they acquire "material new information—not information that was previously available to FDA, nor even cumulative new information that does not add materially to the information that was previously available to the agency." U.S. Br. at 14. This construction of the CBE regulation, which the United

States agrees foreclosed Wyeth from modifying its Phenergan label as required by the Vermont Supreme Court, *id.*, is entitled to substantial judicial deference. *Auer v. Robbins*, 519 U.S. 452, 461 (1997). The United States also agreed with Petitioner that the "direct and positive" language of the Drug Amendments of 1962, Pub. L. No. 87-781, 76 Stat. 780, § 202 ("Section 202"), reflects Congress' desire to preclude field preemption—not to limit conflict preemption analysis "to some subset of conflict preemption." U.S. Br. at 17 (citing *Geier v. Am. Honda Motor Co.*, 529 U.S. 861, 873 (2000)).

2. The United States also implicitly acknowledged that the question presented here satisfies the criteria for review set forth in this Court's Rule 10. As its brief explained, decisions such as that reached by the Vermont Supreme Court conflict with numerous decisions of this Court and, importantly, undermine FDA's "expert determination, based on a careful review of extensive scientific and technical information, that a drug is safe and effective when used according to its labeling, and that the labeling satisfies federal requirements." *Id.* at 9-10. "If [as held by the Vermont Supreme Court] manufacturers were free to make unilateral changes to labeling the day after FDA's approval, based on information that was previously available to FDA, the approval process would be greatly undermined and the agency's careful balancing of risks and benefits thwarted." *Id.* at 12.

3. The United States suggested that the petition should be held because the "decision below does not squarely conflict with any decision of a federal court of appeals or another state supreme court" and because "decisions in two pending FDA preemption cases"—the

Riegel and *Warner-Lambert* cases identified above—"may shed significant light on the question presented in this case." *Id.* at 7-8. Wyeth believes that, to the extent that there is some overlap with issues presented in *Riegel* and *Warner-Lambert*, the Court would benefit from the fuller development of those issues afforded by contemporaneous consideration of this case. Moreover, deciding this case promptly would greatly assist the many lower courts now facing conflict preemption issues in thousands of prescription drug product liability cases.

4. The United States argues that the decision below did not squarely conflict with the California Supreme Court's decision in *Dowhal v. Smithkline Beecham Consumer Healthcare*, 88 P.3d 1 (Cal. 2004), because the *Dowhal* court gave controlling deference to FDA's "specific prohibition of the warnings that would have complied with California law" rather than an FDA labeling decision. U.S. Br. at 19-20. The government speculated that "the Vermont Supreme Court might have found preemption in a case like *Dowhal* even under its erroneous impossibility standard of conflict preemption." *Id.* at 20. Whatever the Vermont Supreme Court might or might not be willing to do in a *Dowhal* situation, however, there remains a square conflict between the California Supreme Court's recognition that states cannot second guess the delicate benefit/risk balances struck by FDA on drug labeling issues and the Vermont Court's willingness to permit a lay jury to override FDA's judgment on the mistaken premise that the "FDCA and the FDA's regulations . . . merely set minimum standards." Pet. at 11a-12a (quoting *McNellis v. Pfizer, Inc.*, No. Civ. 05-1286 JBS, 2005 WL 3752269, at *7 (D.N.J. Dec. 29, 2005)) (internal quotations omitted).

5. A similar fundamental conflict has arisen between the decision below and the Third Circuit's recent decision preempting certain state law advertising claims relating to drug labels in *Pennsylvania Employees Benefit Trust Fund v. Zeneca, Inc.*, 499 F.3d 239, 251 (3d Cir. 2007) (preempting state-law claims because "the purpose of protecting prescription drug users in the FDCA would be frustrated if states were allowed to interpose consumer fraud laws that permitted plaintiffs to question the veracity of statements approved by the FDA"). The Third Circuit thus correctly recognized that the FDA's pervasive drug regulatory powers precluded second-guessing its considered scientific judgments. *Id.* at 251-52. This result led the plaintiffs to file a petition for a writ of certiorari in which they argued that the Third Circuit's preemption decision conflicts with the Vermont Supreme Court's rejection in *Levine* of any conflict between state law duties and "obligations under federal law regulating prescription drug labels." Petition for a Writ of Certiorari, *Penn. Employees Benefit Trust Fund v. Zeneca Inc.*, No. 07-822 (U.S. Dec. 18, 2007) (quoting Pet. at 2a) (internal quotations omitted) ("Penn. Pet.").[1]

6. Indisputably, a deep split in authority persists in the numerous lower court decisions cited in Wyeth's Petition, Pet. at 16 (collecting pre-*Levine* decisions supporting "minimum standards" view of FDCA), as well

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1. Other plaintiffs seeking recovery under state law also are relying on the case below in ongoing litigation. *See, e.g.*, Brief of Appellant, *Conte v. Wyeth*, No. A16707 (Cal. App. 3d Div. Sept. 21, 2007); Brief of Appellant, *McKenney v. Purepac Pharm. Co.*, No. F052606 (Cal. App. 5th Div. Oct. 9, 2007); Brief of Appellant, *Ledbetter v. Merck & Co.*, No. 14-07-00551-CV (Tex. App. 14th Dist. Oct. 17, 2007).

as in cases that have since been decided, *see, e.g.*, *In re Vioxx Prods. Liab. Litig.*, 501 F. Supp. 2d 776, 786 (E.D. La. 2007); *In re Zyprexa Prods. Liab. Litig.*, 489 F. Supp. 2d 230, 275-77 (E.D.N.Y. 2007). Allowing more courts to reject the proper understanding of the FDCA put forward by Petitioner and the United States will only exacerbate an already troubling state of affairs in the lower courts. Although the United States' rejection of the "minimum standards" view of the FDCA and of the Vermont Supreme Court's misconstruction of the CBE regulation should be determinative, it gives little real assurance against continuing error in the vast majority of lower court cases. Pet. at 29 (collecting cases denying deference to FDA's interpretation of FDCA and its implementing regulations). Review by the Court during this Term would advance important interests of judicial economy and efficiency, for it will provide the lower courts with guidance on an important legal issue that is likely to affect thousands of pending cases.

7. Given the multiplicity and importance of prescription drug product liability cases, calendaring this case for argument so that it may be considered contemporaneously with *Riegel* and *Warner-Lambert* would enrich this Court's consideration of such potentially overlapping issues as the "floor and ceiling" characteristics of the Medical Device Amendments ("MDA") to FDCA and FDCA drug approval regimes, and their limitations on post-approval labeling changes.[2]

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2. While the United States noted that *Warner-Lambert* "involves implied preemption of claims involving FDA's approval of a new drug application," U.S. Br. at 22, the principal focus of that case is whether state statutory immunity from tort liability

(Cont'd)

Simultaneous review will allow the Court to consider fully whether there is any meaningful difference between MDA statutory preemption and conflict preemption under FDCA, a question that repeatedly arose during the *Riegel* oral argument. Oral Argument Transcript at 8-12, 25, 44, *Riegel v. Medtronic, Inc.*, No. 06-179 (U.S. Dec. 4, 2007). Indeed, given the routine and mistaken failure of a number of lower courts to apply clearly analogous MDA precedent in resolving FDCA preemption issues, it is essential that the Court speak directly to FDCA preemption as well as MDA preemption. *See, e.g., In re Vioxx Prods. Liab. Litig.*, 501 F. Supp. 2d at 784; *Caraker v. Sandoz Pharms. Corp.*, 172 F. Supp. 2d 1018, 1041-42 (S.D. Ill. 2001); *Cartwright v. Pfizer, Inc.*, 369 F. Supp. 2d 876, 885 (E.D. Tex. 2005).

8. Moreover, the applicability and meaning of Section 202, which was central to the Vermont Supreme Court's truncated preemption analysis here, is not presented in *Riegel*. Only this Court's authoritative construction of Section 202 and the CBE regulation will provide the necessary, definitive guidance in the thousands of drug labeling cases pending in the lower courts. *See, e.g.*, Penn. Pet. at 32 (arguing that the "phrase 'direct and positive conflict' demonstrates that Congress intended *not* to pre-empt state-law claims").

(Cont'd)

for prescription drugs labeled in accordance with FDA approval can include an exclusion for fraud on FDA, a dispute that turns on the meaning of this Court's decision in *Buckman Co. v. Plaintiffs' Legal Committee*, 531 U.S. 341 (2001). Thus, as the United States recognized, *Warner-Lambert* is unlikely to resolve the question presented here.

9. At base, the United States has advanced a powerful, and indeed unassailable, paradigm for FDA preemption that necessitates reversal here: "Because respondent's claims challenge labeling that FDA approved after being informed of the relevant risk, they conflict with FDA's approval of the labeling and are therefore preempted." U.S. Br. at 8. This view of the FDCA and FDA's implementing regulations, however, has met stiff resistance in the lower courts. This Court should grant the petition and schedule the case for review this Term to properly conclude this longstanding debate.

CONCLUSION

For the foregoing reasons, Petitioner respectfully requests that the Court grant the petition for a writ of certiorari.

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78

IN THE
Supreme Court of the United States

WYETH,

Petitioner,

v.

DIANA LEVINE,

Respondent.

On Petition for a Writ of Certiorari to the
Supreme Court of Vermont

RESPONDENT'S SUPPLEMENTAL BRIEF IN RESPONSE TO BRIEF OF THE UNITED STATES

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RESPONDENT'S SUPPLEMENTAL BRIEF IN RESPONSE TO BRIEF OF THE UNITED STATES

Seven full months after being invited to do so, the Solicitor General has provided the views of the United States on this case. The Solicitor General agrees with respondent Diana Levine that there is no division among the federal or state appellate courts on the question presented. Indeed, he acknowledges that no appellate court has ever held that a state-law claim for damages based on a drug manufacturer's failure to warn of a prescription drug hazard is preempted by the Food, Drug, and Cosmetic Act (FDCA). And he does not claim that the decision below conflicts with a decision of this Court on the same or even a similar question.

The Solicitor General also agrees with Ms. Levine that the Vermont Supreme Court found that the FDA did not consider for inclusion in Phenergan's labeling, let alone reject, the warning that Ms. Levine maintains would have prevented her life-altering injuries. And although the federal government is in a position to know exactly what the FDA did or did not consider, the Solicitor General nowhere even suggests that the Vermont Supreme Court's finding is incorrect. Finally, the Solicitor General does not argue that this case presents one of those rare cases demanding error correction. That argument would make no sense because, for seven decades, state-law tort liability of the kind affirmed by the Vermont Supreme Court has co-existed with FDA approval of prescription drugs — again, without *any* appellate authority to the contrary.

Therefore, as one would expect, because this case meets none of the Court's time-honored criteria for granting review, the Solicitor General does not recommend that the petition be granted. Nonetheless, he urges that the petition be held pending the Court's decisions in two cases — one an express preemption case involving a medical device (not a drug) and the other a case involving the preemption implications of a unique

Michigan "tort reform" statute — neither of which is likely to have any bearing on the question presented here.

The petition should be denied — and it should be denied *now*.[1]

A. The Pendency of *Riegel* and *Warner-Lambert* Provides No Basis To Hold The Petition.

The Solicitor General is wrong in maintaining that the petition should be held pending the Court's rulings in *Riegel v. Medtronic, Inc.*, No. 06-179 (argued Dec. 4, 2007), and *Warner-Lambert, LLC v. Kent*, No. 06-1498 (to be argued Feb. 25, 2008). Neither case is likely to inform the proper disposition of this case.

The issue in *Riegel* is distinct from the question here for two related reasons. First, *Riegel* presents a preemption question under the FDCA's Medical Device Amendments (MDA), not its prescription drug provisions. Medical devices are regulated differently from drugs. The MDA contains many provisions — concerning, for instance, adverse event reporting by user facilities, product recall, and subpoena power, and a savings clause, 21 U.S.C. § 360h(d) — that do not apply to drugs and may bear on the preemption question in *Riegel*.

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[1]The Solicitor General's brief focuses mainly on the merits, taking the extreme position that FDA approval of a drug generally preempts *all* state-law claims regarding the drug's safety, efficacy, or labeling. SG Br. 8. The Solicitor General's view of the merits does not bear on the question whether the petition should granted. We note only that no appellate or trial court in history has ever adopted the Solicitor General's position. *See* Opp. 13 & n.3 (explaining that no appellate court has endorsed even Wyeth's less expansive position). And we reiterate that, just last year, the FDA filed briefs that took a considerably less radical view. *See id.* at 19 n.6. Indeed, the Solicitor General acknowledged that his brief takes a position that goes beyond any position previously articulated by the FDA. SG Br. 18.

Second, *Riegel* presents *only* the question whether the MDA's *express* preemption clause, 21 U.S.C. § 360k(a), preempts certain state-law claims. *See* Pet. for Cert. in *Riegel*, No. 06-79, at i ("Whether the express preemption provision of the Medical Device Amendments to the Food, Drug, and Cosmetic Act, 21 U.S.C. § 360k(a), preempts state-law claims seeking damages for injuries caused by medical devices that received premarket approval from the Food and Drug Administration."). This case, on the other hand, involves only *implied* preemption, as the FDCA contains no express preemption provision with respect to prescription drugs. Over a decade ago, the Court decided *Medtronic, Inc. v. Lohr*, 518 U.S. 470 (1996), which set forth the parameters of express preemption of state-law tort claims under the MDA. Since then, not a single appellate decision has suggested, let alone held, that the analysis in *Lohr* bears on the question whether the FDCA preempts state-law claims involving prescription drugs.

As in *Lohr*, the Court's focus in *Riegel* will be on the text of the MDA's express preemption clause and the FDA's regulations promulgated under that clause, and *not* on the implied preemption question here: whether the FDCA as a whole evinces an unspoken intent to preempt Ms. Levine's claims on the ground that those claims somehow conflict with the objectives of federal prescription drug regulation. The Solicitor General (at 21) asserts that, in *Lohr*, "this Court ... determined that implied preemption principles are relevant to the interpretation" of the MDA's preemption clause provision, but the portion of *Lohr* he cites for that proposition proves *our* point: It contains an almost word-by-word textual analysis of the MDA's preemption clause, 21 U.S.C. § 360k(a), and the FDA regulation promulgated thereunder, 21 C.F.R. § 808.1(d), *see Lohr*, 518 U.S. at 500 — an analysis that is irrelevant to the

question whether the FDCA impliedly preempts a state-law claim involving a prescription drug.[2]

Similarly, the Solicitor General is wrong that the Court's decision in *Warner-Lambert* will prove relevant here. *Warner-Lambert* involves a Michigan statute that precludes, *as a matter of state law*, any tort claim arising from a defective or inadequately labeled prescription drug if that drug was approved for marketing by the FDA and its labeling complied with that approval at the time it was marketed. Mich. Comp. Laws § 600.2946(5). The Michigan law contains a narrow exception to this state-law defense if the manufacturer intentionally withheld information from the FDA, or misrepresented information to the FDA, that was required to be submitted to the agency, *and* the agency would not have approved the drug or would have withdrawn the drug's approval if the proper information had been submitted. *Id.* § 600.2946(5)(a). The question presented in *Warner-Lambert* is only whether a Michigan tort plaintiff's attempt to make the showings necessary to avoid the defense provided by the Michigan statute is preempted by federal law.

The narrow issue in *Warner-Lambert* has nothing to do with this case. The issue here — whether a traditional common-law damages claim premised on a drug's inadequate labeling is preempted by the FDCA — is exactly the issue taken off the table *as a matter of state law* by the Michigan statute, which

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[2]This Court's decisions have demonstrated that claims of express and implied preemption demand analytically distinct analyses. *See, e.g., Bates v. Dow Agrosciences LLC*, 544 U.S. 431, 458-59 (2005) (Thomas, J., concurring) (making this point and noting "this Court's increasing reluctance to expand federal statutes beyond their terms through doctrines of implied pre-emption"); *Sprietsma v. Mercury Marine*, 537 U.S. 51 (2002) (conducting entirely separate implied and express preemption analyses); *Lohr*, 518 U.S. at 503.

generally provides a defense to such a claim. Therefore, that issue, by definition, cannot be presented in *Warner-Lambert*. And put the other way around, the issue that *is* presented in *Warner Lambert* has no bearing on this case because Ms. Levine was not was required by state law to make the showings demanded by the exception to Michigan's unique statute. Her claim rested entirely on Wyeth's failure to adequately instruct doctors and patients about administration of Phenergan. It did not depend on whether the FDCA required particular information to be submitted to the FDA, whether Wyeth failed to provide that information to the FDA, or what the FDA would or would not have done had it received that information.

In sum, neither *Riegel* nor *Warner-Lambert* provides any reason for holding the petition.

B. The Solicitor General's Brief Underscores Wyeth's Attempt To Seek Review On A Question Not Genuinely Presented By This Case.

The question presented by Wyeth is whether the "labeling judgments" made by the FDA regarding a drug's safety and efficacy preempt state-law product liability claims premised on "differing label judgments." Pet. i. Our opposition explains (at 14-21) that this case does not genuinely present that question because the Vermont Supreme Court correctly found, as a matter of fact, that Ms. Levine's recovery was *not* based on a labeling judgment different from a labeling judgment made by the FDA. Wyeth's claim for preemption rests on its assertion that the FDA had specifically considered and rejected a label change that would have prohibited IV-push administration of Phenergan. But the Vermont Supreme Court rejected that argument as having *no factual basis in the record*, *see* Pet. App. 17a-19a, and the Solicitor General takes no issue with that finding. Thus, before the Court could resolve the question presented, Wyeth would have to convince it to take two highly

unusual steps: first, to grant review "when the asserted error consists of erroneous factual findings," S. Ct. Rule 10, and, then, to overturn the Vermont Supreme Court's factual findings.

The Solicitor General recognizes that, in its present posture, this case does not present the question that *Wyeth* has posed. He acknowledges that the Vermont Supreme Court's holding is based on that court's "findings of fact," and that for Wyeth to prevail on *its* question presented it must "dispute the Vermont Supreme Court's interpretation of the record in this case." SG Br. 20. In other words, the Solicitor General realizes that the question as stated by Wyeth is not cert-worthy. So, undeterred by the disconnect between the Vermont Supreme Court's findings and Wyeth's question presented, the Solicitor General has changed the question presented to make the Vermont's factual findings irrelevant. *See id.* at (I). He says that it makes no difference whether the FDA even considered, let alone rejected, a label warning that would have precluded IV-push administration. *Id.* at 20. As long as the FDA had before it information regarding the "relevant risk" — and, according to the Solicitor General, that means here only the highly general risk of arterial exposure to Phenergan injection, *id.* at 14 — FDA approval of a drug "preempts state law claims challenging the drug's safety, efficacy, or labeling." *Id.* at 8. Putting aside the Solicitor General's unprecedented view of preemption, *see supra* note 1, his attempt to alter the question presented is improper and serves only to underscore that the *actual* question presented is not before the Court unless it first overturns the Vermont Supreme Court's factual findings.[3]

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[3]The Solicitor General must know that those factual findings will not be overturned by this Court. The FDA — whose General Counsel appears on the Solicitor General's brief — knows what it did with respect to the Phenergan label, and the Solicitor General's brief does not contest the

(continued...)

For its part, even Wyeth does not embrace the Solicitor General's all-encompassing view of preemption. To the contrary, its appellate counsel (who remains counsel of record in this Court) stated at oral argument in the Vermont Supreme Court that

> I want to emphasize to the Court that the issue as presented here is very narrow and very particularized. . . . It's focused on Phenergan in the facts of this case. Wyeth is not contending for field preemption, for the ouster of Vermont law, tort law [is] not at issue here . . . nor are we arguing that the mere compliance with federal labeling requirements in and of itself creates a conflict preemption.

Vt. S. Ct. Oral Arg. Tr. 7 (Oct. 5, 2005). The Solicitor General's view of preemption is anything but "narrow and particularized." In his view, "mere compliance with federal labeling requirements" *does* "in and of itself create . . . conflict preemption." *See* SG Br. 8. Not only does Wyeth not present that question in its petition, but its counsel affirmatively waived any broader argument in the court below.

In sum, the case presents neither the question as framed by Wyeth nor the broader question that the Solicitor General would prefer. For these reasons, review should be denied.

C. Recent FDCA Amendments Provide Another Reason To Deny Review.

An amendment to the FDCA enacted after the petition and opposition were filed provides another reason to deny review.

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[3](...continued)
Vermont Supreme Court's finding that "[t]here is no evidence that the FDA intended to prohibit defendant from strengthening the Phenergan label" with an instruction precluding IV push. Pet. App. 19a.

On September 27, 2007, Congress passed the Food and Drug Administration Amendments Act of 2007 (FDAAA), Pub. L. No. 110-85, 121 Stat. 823. Section 901(a) of FDAAA bolsters the FDA's authority to require a manufacturer to change a drug label if the agency becomes aware of information that it believes should be included in the label. 121 Stat. at 924 (to be codified at 21 U.S.C. § 355(o)(4)). This provision does not alter drug companies' longstanding statutory and regulatory obligations to revise inadequate labels and to seek agency approval of label changes even in the absence of an agency demand. Nonetheless, in an apparent effort to ward off any future claim of preemption, section 901(a) includes a "rule of construction":

> This paragraph shall not be construed to affect the responsibility of the responsible person or the holder of the approved application under section 505(j) to maintain its label in accordance with existing requirements, including subpart B of Part 201 and sections 314.70 and 601.12 of Title 21, Code of Federal Regulations (or any successor regulations).

121 Stat. at 925-26 (to be codified at 21 U.S.C. § 355(o)(4)(I)). By establishing that the FDA's new authority to order label changes does not alter manufacturers' existing obligations to assure that labels promote patient safety, the rule of construction underscores the importance of 21 C.F.R. § 314.70(c)(6), which allows manufacturers to amend labels to strengthen warnings and instructions and to add contraindications without FDA pre-approval, and 21 C.F.R. § 201.80(e), which provides that drug "labeling shall be revised to include a warning as soon as there is reasonable evidence of an association of a serious hazard with a drug."

Section 901(a)'s legislative history indicates that the "rule of construction" was motivated by a desire to assure that the

FDA's new authority to demand label changes would not preempt future damages claims. *See* 153 Cong. Rec. S11832, col. 3 - S11833, cols. 1-2 (Sept. 20, 2007) (Sen. Kennedy); *id.* at S11834, cols. 2-3 (Sen. Leahy); *id.* at S11835, col. 3 (Sen. Durbin). Indeed, even a senator who would have preferred statutory language that would have "occupied the field" of drug labeling and preempted damages suits construed the rule of construction as having anti-preemptive effect, thereby "open[ing] the floodgates" for suits and affording "a definite boon for trial lawyers." *Id.* at S11836, col. 3 - S11837, col. 1 (Sen. Allard).

As noted, we believe that the rule of construction underscores Congress's view that, in the future, state-law damages liability should continue to co-exist with the FDA's enhanced power to demand label changes. But that question will be fiercely debated in case after case. Indeed, the issue has already been briefed in one multi-district case, *In re Seroquel Products Liability Litigation*, MDL 1769 (M.D. Fla.). *See also* Arnold & Porter LLP, Client Advisory — The FDA Amendments Act of 2007, at 9, available at http://www.arnoldandporter.com/resources/documents/A&PCA_ExecutiveSummary-TheFDA_Oct107_V2.pdf (noting that the rule of construction is "undoubtedly a tool that will be used by plaintiffs seeking to undermine preemption in 'failure to warn' cases").

The meaning of the rule of construction is not, of course, at issue in *Riegel* or *Warner-Lambert*. Nor is it at issue in Ms. Levine's case, which unfolded years before the FDAAA was enacted. But it *will be* at issue in future cases presenting the question whether the FDCA preempts state-law failure-to-warn claims regarding prescription drugs. And if the Court wishes to address that issue, despite the absence of a conflict among the lower courts, it should await input from those courts on the

meaning of the FDAAA and a case, unlike Ms. Levine's, in which the FDAAA actually applies.

CONCLUSION

In most cases, the facts of the litigants' personal circumstances are properly disregarded in deciding whether to grant review. But here — where petitioner Wyeth's claim for review is fundamentally a challenge to the lower courts' factual findings and the Solicitor General's claim for further delay is based on an unabashed effort to rewrite the question presented — Ms. Levine's circumstances should not be ignored. Diana Levine lost her arm and her livelihood nearly eight years ago. In 2004, she won a verdict compensating her for undisputed future medical expenses and lost income. Wyeth filed its petition in March 2007 and the Court called for the Solicitor General's views the next month. The Solicitor General did not respond for seven months. When he did, he *agreed* that the case was not worthy of review, but nevertheless requested further delay — based solely on speculation that pending cases presenting different questions might somehow affect the proper resolution of this case. All the while, unable to collect her judgment, Ms. Levine faces massive and ever-mounting medical debt.

Under these circumstances, enough is enough. As we said at the outset, the petition should be denied — and it should be denied *now*.

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January 2, 2008

(4)

No. 06-1249

In the Supreme Court of the United States

WYETH, PETITIONER

v.

DIANA LEVINE

ON WRIT OF CERTIORARI TO THE SUPREME COURT OF VERMONT

BRIEF FOR THE UNITED STATES AS AMICUS CURIAE SUPPORTING PETITIONER

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QUESTION PRESENTED

Whether the prescription drug labeling judgments imposed on manufacturers by the Food and Drug Administration (FDA) pursuant to FDA's comprehensive safety and efficacy authority under the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. 301 *et seq.*, preempt state law product liability claims premised on the theory that different labeling judgments were necessary to make drugs reasonably safe for use.

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In the Supreme Court of the United States

No. 06-1249

WYETH, PETITIONER

v.

DIANA LEVINE

ON WRIT OF CERTIORARI TO THE SUPREME COURT OF VERMONT

BRIEF FOR THE UNITED STATES AS AMICUS CURIAE SUPPORTING PETITIONER

INTEREST OF THE UNITED STATES

This case concerns the extent to which state law may hold a drug manufacturer liable for using labeling approved by the federal Food and Drug Administration (FDA). FDA administers the approval process for new drugs and monitors the safety of approved drugs after they have been marketed. At the Court's invitation, the United States filed a brief as amicus curiae at the petition stage of this case.

STATEMENT

1. Under the Federal Food, Drug, and Cosmetic Act (FDCA or Act), 21 U.S.C. 301 *et seq.*, a drug manufacturer may not market a new drug unless it has submitted a new drug application to the Food and Drug Administration (FDA) and received the agency's approval. 21

U.S.C. 355(a). An application must contain, among other things, "the labeling proposed to be used for such drug," 21 U.S.C. 355(b)(1)(F) (Supp. V 2005); see 21 C.F.R. 314.50(c)(2)(i) and (e)(2)(ii); "full reports of investigations which have been made to show whether or not such drug is safe for use and whether such drug is effective in use," 21 U.S.C. 355(b)(1)(A) (Supp. V 2005); and "a discussion of why the benefits exceed the risks [of the drug] under the conditions stated in the labeling," 21 C.F.R. 314.50(d)(5)(viii); see 21 C.F.R. 314.50(c)(2)(ix).

The FDCA also requires that drugs not be misbranded. 21 U.S.C. 331(a) and (b). A drug is misbranded if, among other things, its "labeling is false or misleading in any particular;" the labeling does not provide "adequate directions for use" or certain "adequate warnings;" or the drug "is dangerous to health when used in the dosage or manner, or with the frequency or duration prescribed, recommended, or suggested in the labeling thereof." 21 U.S.C. 352(a), (f) and (j). FDA has established specific requirements for drug labeling. 21 C.F.R. Pt. 201.

FDA will approve a new drug application only if it finds, among other things, that (i) the drug is "safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof," (ii) there is "substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling thereof," and (iii) the proposed labeling is not "false or misleading in any particular." 21 U.S.C. 355(d).

After a drug has been approved and marketed, the manufacturer must investigate and report to FDA any adverse events associated with the use of the drug in

humans, 21 C.F.R. 314.80, and must periodically submit any new information that may affect FDA's previous conclusions about the safety, effectiveness, or labeling of the drug, 21 C.F.R. 314.81. See 21 U.S.C. 355(k); Food and Drug Administration Amendments Act of 2007 (FDAAA), Pub. L. No. 110-85, § 901, 121 Stat. 922 (enhancing FDA's authority to require postmarket clinical studies, clinical trials, and surveillance). FDA "shall" withdraw its approval of an application if it finds, among other things, that the drug is not safe or effective under the conditions of use specified in the drug's labeling. 21 U.S.C. 355(e).

Following FDA's approval of an application, the manufacturer generally may not make changes to the drug, including "[c]hanges in labeling," without first submitting a supplemental application to FDA and securing the agency's prior approval for the change. 21 C.F.R. 314.70(b)(2)(v)(A). A manufacturer must submit such a supplemental application "to include a warning about a clinically significant hazard as soon as there is reasonable evidence of a causal association with a drug." 21 C.F.R. 201.57(c)(6). "An applicant may ask FDA to expedite its review of a supplement for public health reasons." 21 C.F.R. 314.70(b)(4). A manufacturer may, however, change a drug's labeling after its supplemental application is received by FDA, without waiting for the agency's approval of the change, if, among other things, the change "add[s] or strengthen[s]" a warning or a statement about administration of the drug in order to promote safety. 21 C.F.R. 314.70(c)(6)(iii)(A) and (C).[1]

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[1] The FDCA itself does not directly address changes to a drug's labeling after a new drug application has been approved. That subject is instead left to FDA to address by regulation. Compare 21

FDA interprets that regulation to permit changes without prior approval only to address "newly discovered risks" for which there is sufficient evidence of causal association with the drug. See 47 Fed. Reg. 46,623 (1982); 73 Fed. Reg. 2848 (2008) (proposing to codify that interpretation). If a manufacturer makes such a change before receiving FDA's approval, the agency may later disapprove the change and order the manufacturer to cease distribution of the changed product. 21 C.F.R. 314.70(c)(7).

2. After FDA approved petitioner's new drug application for the anti-nausea drug Phenergan, petitioner informed FDA of adverse events in which Phenergan apparently was inadvertently injected intra-arterially, resulting in gangrene and amputation. See, *e.g.*, Pet. App. 139a-140a (1967 report). Over the ensuing years, FDA and petitioner engaged in back-and-forth communications concerning the appropriate labeling to address the risks presented by inadvertent intra-arterial injection. See, *e.g.*, *id.* at 141a-166a. As part of its deliberations, FDA convened an expert advisory committee to consider that question. *Id.* at 144a, 147a-148a. FDA was thus fully aware of the risk of an inadvertent intra-arterial injection, and the labeling or revised labeling it approved uniformly contained warnings to address that risk. See, *e.g.*, *id.* at 142a-143a, 151a-154a, 162a, 165a; J.A. 271, 276, 277, 282, 283, 311-312, 356, 359, 374, 382, 390-391.

As of 2000 (when the events giving rise to this suit occurred), the FDA-approved labeling stated, in part, that "[u]nder no circumstances should Phenergan Injec-

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U.S.C. 360e(d)(6) (addressing certain changes to an approved medical device).

tion be given by intra-arterial injection due to the likelihood of severe arteriospasm and the possibility of resultant gangrene." Pet. App. 167a. The labeling went on to explain that the "preferred" method of administering the drug is "by deep intramuscular injection," because intravenous administration can result, in some circumstances, in inadvertent intra-arterial injection. *Ibid.* For circumstances in which the drug is injected intravenously, the labeling described in detail how such injection should be done, in order "to avoid * * * inadvertent intra-arterial injection." *Ibid.*; see *id.* at 4a-5a n.1.

3. In April 2000, respondent sought treatment at a health center for headache and nausea. Pet. App. 2a. The health center's staff first administered Phenergan to respondent by intra-muscular injection. *Ibid.* When respondent's nausea continued, the staff administered an additional dose of Phenergan later the same day by intravenous injection into her arm. *Ibid.* The intravenous injection was made by a procedure the parties refer to as IV push, whereby the staff did not drip the Phenergan solution through a free-flowing bag into a tube already inserted into respondent's arm, but instead sought to inject it directly into a vein in her arm. See *id.* at 2a, 52a. The IV push apparently resulted in inadvertent arterial injection, which caused gangrene and required amputation of respondent's hand and forearm. *Id.* at 2a.

Respondent brought and settled an action against the health center where she had received the injection of Phenergan. Pet. App. 50a. She also sued petitioner in a Vermont state court, asserting negligence and failure-to-warn claims premised on alleged inadequacies in the drug's labeling. *Id.* at 3a. Respondent asserted that "the label should not have allowed IV push as a means of

administration, as it was safer to use other available options, such as intramuscular injection or administration through the tubing of a hanging IV bag." *Ibid.* After the trial court rejected petitioner's preemption defense, *id.* at 51a-65a, the jury found in respondent's favor, and the trial court entered judgment in the amount of $6,774,000, *id.* at 3a.

4. a. The Supreme Court of Vermont affirmed. Pet. App. 1a-34a. It interpreted 21 C.F.R. 314.70(c) "to allow unilateral changes to drug labels whenever the manufacturer believes it will make the product safer." *Id.* at 13a. The court viewed that section as crucial to its preemption analysis: "While specific federal labeling requirements and state common-law duties might otherwise leave drug manufacturers with conflicting obligations, [Section] 314.70(c) allows manufacturers to avoid state failure-to-warn claims without violating federal law" by making unilateral changes to FDA-approved labeling. *Id.* at 11a.

The Vermont Supreme Court also relied on a provision in the 1962 amendments to the FDCA that states that "[n]othing in the amendments * * * shall be construed as invalidating any provision of State law * * * unless there is a direct and positive conflict between such amendments and such provision of State law." Drug Amendments of 1962, Pub. L. No. 87-781, § 202, 76 Stat. 793. The court construed that provision to limit preemption to circumstances in which it would be physically impossible for a manufacturer to comply with both federal and state law. Pet. App. 21a. Here, the court determined, there was no such impossibility because the record did not affirmatively show that FDA would have rejected a supplemental application seeking to strengthen the warning. *Id.* at 17a.

b. Chief Judge Reiber dissented. Pet. App. 35a-48a. He explained that respondent's state-law claims conflict with federal law because, while "FDA concluded that the drug—with its approved methods of administration and as labeled—was both safe and effective," the "jury concluded that the same drug—with its approved methods of administration and as labeled—was 'unreasonably dangerous.'" *Id.* at 35a (quoting *Town of Bridport* v. *Sterling Clark Lurton Corp.*, 693 A.2d 701, 704 (Vt. 1997)). Supporting that conclusion, in the Chief Judge's view, was the fact that FDA does not merely establish minimum safety standards, but instead "balances its assessment of a drug's safety against concerns for the drug's efficacy, taking into account that a safer but less effective drug is not necessarily best for the public health overall." *Id.* at 47a. With respect to drug labels, the Chief Judge explained, "FDA considers not only what information to include, but also what to exclude," in part because overwarning can do more harm than good. *Ibid.*

The Chief Judge also took issue with the majority's understanding of Section 314.70(c). Pet. App. 39a-41a. He explained that the regulation "allow[s] manufacturers to address newly-discovered risks," but "does not allow manufacturers to simply reassess and draw different conclusions regarding the same risks and benefits already balanced by the FDA." *Id.* at 40a.

SUMMARY OF ARGUMENT

Respondent's claims are preempted because they challenge labeling that FDA approved after being informed of the relevant risk.

A. FDA approves new drugs based on a thorough evaluation of their safety, efficacy, and labeling. The

agency's consideration of safety and effectiveness is directly tied to its consideration of proposed labeling, because a drug's safety and effectiveness depend on the conditions under which it is used (such as its dosage, method of administration, and intended use). Many drugs can be dangerous if not used as directed, and labeling can help ameliorate risks of misuse. As part of the new-drug approval process, FDA considers and approves specific labeling for a drug, and the drug manufacturer is generally barred from making unilateral changes to the FDA-approved labeling.

In deciding whether to approve a drug, FDA does not merely establish minimum standards of safety. Instead, as with the Class III medical devices at issue in *Riegel* v. *Medtronic, Inc.*, 128 S. Ct. 999 (2008), FDA weighs a drug's health benefits against its health risks, and "generally considers a drug safe when the expected therapeutic gain justifies the risk entailed by its use." *United States* v. *Rutherford*, 442 U.S. 544, 555 (1979). FDA also balances the health benefits and detriments of particular labeling, in part because labeling must strike a balance between notifying users of potential dangers and not unnecessarily deterring beneficial uses through overwarning. If FDA concludes that a drug's benefits outweigh its risks only under certain conditions, the agency may require appropriate labeling to reflect that determination.

B. Because FDA's approval strikes a balance between competing considerations, state laws that strike a different balance conflict with FDA's determination and are impliedly preempted. In *Riegel*, this Court determined that "[s]tate tort law that requires a manufacturer's [devices] to be safer, but hence less effective, than the model the FDA has approved disrupts the fed-

eral scheme." 128 S. Ct. at 1008. So too here, state tort law that required a manufacturer to use different labeling than that approved by FDA would disrupt the agency's balancing of health risks and benefits. The FDA-approved labeling gives specific instructions on how to inject Phenergan intravenously; respondent, in contrast, would impose further limits on such injection—limits that might harm some patients' health by restricting their physicians' treatment options. If a state regulatory agency directed drug manufacturers not to use FDA-approved labeling, the conflict with federal law would be manifest. As in *Riegel*, the fact that juries instead of an expert agency would second-guess FDA's judgments in individual cases only exacerbates the conflict.

C. The Vermont Supreme Court opined that an FDA regulation, 21 C.F.R. 314.70(c), "allow[s] unilateral changes to drug labels whenever the manufacturer believes [the changes] will make the product safer." Pet. App. 13a. That interpretation of the regulation is wrong, because Section 314.70(c) permits manufacturers to make changes to the labeling, subject to FDA's subsequent review and approval, based *only* on newly available information, not based on information that was previously submitted to FDA—let alone whenever the manufacturer believes a different label "will make the product safer." If manufacturers were free to make unilateral changes to labeling the day after FDA's approval, based on information that was previously available to FDA, the approval process would be undermined and the agency's careful balancing of risks and benefits as reflected in the labeling would be thwarted. Here, there is no question that petitioner informed FDA of the relevant risk, and FDA determined that Phenergan was safe

and effective under the conditions set forth in the labeling, including intravenous administration.

D. The Vermont Supreme Court also erred in concluding that normal conflict-preemption principles do not apply to the FDCA. The 1962 amendments to the FDCA provide that they should not "be construed as invalidating any provision of State law * * * unless there is a direct and positive *conflict* between such amendments and such provision of State law." Pub. L. No. 87-781, § 202, 76 Stat. 793 (emphasis added). That provision means that the relevant amendments do not give rise to *field* preemption; it does not express any intent to preserve state laws that *conflict* with federal law, as Vermont tort law does in this case.

ARGUMENT

THE FDCA PREEMPTS TORT CLAIMS THAT WOULD IMPOSE LIABILITY FOR THE USE OF LABELING THAT THE FOOD AND DRUG ADMINISTRATION APPROVED AFTER BEING INFORMED OF THE RELEVANT RISK

Federal law preempts state laws that conflict with federal law, including state laws that either "make it 'impossible' for private parties to comply with both state and federal law," *Geier* v. *American Honda Motor Co.*, 529 U.S. 861, 873 (2000), or that "stand[] as an obstacle to the accomplishment and execution of the full purposes and objectives of Congress," *Hines* v. *Davidowitz*, 312 U.S. 52, 67 (1941). Because respondent's claims challenge labeling that FDA approved after being informed of the relevant risk (and that petitioner was not free to change in the manner urged by respondent without FDA's prior approval), they conflict with FDA's approval of the labeling and are preempted.

A. FDA's Approval Of A Drug, Including Its Labeling, Reflects The Agency's Expert Weighing Of The Health Risks And Benefits Of The Drug As Labeled

1. FDA may approve a new drug application only if it determines, among other things, that (i) the drug is "safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof," (ii) there is "substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling thereof," and (iii) the proposed labeling is not "false or misleading in any particular." 21 U.S.C. 355(d). The agency's consideration of safety and effectiveness is directly tied to its consideration of "the proposed labeling," *ibid.*, because a drug's safety and effectiveness usually depend on the conditions under which it is used (such as its dosage, its method of administration, and its intended use). Thus, "[d]rug labeling serves as the standard under which FDA determines whether a product is safe and effective." 50 Fed. Reg. 7470 (1985). Labeling is "[t]he centerpiece of risk management," as it "communicates to health care practitioners the agency's formal, authoritative conclusions regarding the conditions under which the product can be used safely and effectively." 71 Fed. Reg. 3934 (2006); cf. *Riegel* v. *Medtronic, Inc.*, 128 S. Ct. 999, 1004 (2008) ("FDA evaluates safety and effectiveness [of Class III medical devices] under the conditions of use set forth on the label.").

FDA's review of a new drug application is similar to its premarket approval process for Class III medical devices, see 60 Fed. Reg. 39,180 (1995), which this Court has described as "rigorous," *Riegel*, 128 S. Ct. at 1004;

see *id.* at 1018 (Ginsburg, J., dissenting); *Medtronic, Inc.* v. *Lohr*, 518 U.S. 470, 477 (1996). "Under the FDCA, a drugmaker must submit research data to FDA at two general stages of new-drug development." *Merck KGaA* v. *Integra Lifesciences I, Ltd.*, 545 U.S. 193, 196 (2005). A manufacturer first submits an investigational new drug application seeking authorization to conduct clinical trials (*i.e.*, trials on humans) in order to investigate the safety and effectiveness of the drug. See 21 U.S.C. 355(i) (2000 & Supp. V 2005); 21 C.F.R. 312.20. In determining whether to permit clinical trials to proceed, FDA considers whether "the drug involved represents an unreasonable risk to the safety of the persons who are the subjects of the clinical investigation." 21 U.S.C. 355(i)(3)(B)(i). The investigational new drug application must be supported by pre-clinical research regarding the safety and efficacy of the drug, including "pharmacological and toxicological studies of the drug involving laboratory animals or in vitro." 21 C.F.R. 312.23(a)(8); see generally 21 C.F.R. 312.23(a).

If clinical trials demonstrate safety and efficacy, a manufacturer may submit a new drug application seeking approval to market the drug. See 21 U.S.C. 355(b) (2000 & Supp. V 2005). The applicant must submit "the labeling proposed to be used for such drug," 21 U.S.C. 355(b)(1)(F) (Supp. V 2005), as well as extensive information about the composition, manufacture, and specification of the drug, the pre-clinical and clinical studies, and "any other data or information relevant to an evaluation of the safety and effectiveness of the drug product obtained or otherwise received by the applicant from any source." 21 C.F.R. 314.50(d)(5)(iv); see 21 U.S.C. 355(b)(1)(A) (Supp. V 2005). FDA has issued numerous guidance documents that describe, in detail, how to pre-

pare a new drug application. See FDA, *Drug Applications, New Drug Application (NDA) Process* (last modified Dec. 28, 2007) <http://www.fda.gov/cder/regulatory/applications/NDA.htm> (listing the guidance documents).

FDA must deny any application that does not "include adequate tests by all methods reasonably applicable to show whether or not such drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling." 21 U.S.C. 355(d)(1). There must also be "substantial evidence" of the drug's effectiveness, with "substantial evidence" defined to be "adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have." 21 U.S.C. 355(d).

FDA's "rigorous evaluation process * * * scrutinizes everything about the drug—from the design of clinical trials to the severity of side effects to the conditions under which the drug is manufactured." FDA, *The FDA's Drug Review Process: Ensuring Drugs Are Safe and Effective* (*Review Process*) (visited June 2, 2008) <http://www.fda.gov/fdac/special/testtubetopatient/drugreview.html>. "[A]n FDA review team—medical doctors, chemists, statisticians, microbiologists, pharmacologists, and other experts—evaluates whether the studies the sponsor submitted show that the drug is safe and effective for its proposed use." *Ibid.* In order to ensure that FDA has all the information it needs, the agency "usually communicates often with sponsors about scientific, medical, and procedural issues that arise dur-

ing the review process." FDA, *The CDER Handbook* 24 (1998) <http://www.fda.gov/cder/handbook/handbook.pdf>; see 21 C.F.R. 314.50(f)(4), 314.102(a), (c), (d), and (e). FDA may also consult with independent panels of scientific experts. 21 U.S.C. 355(n). FDA is more likely to consult with such an independent advisory committee if a drug is the first in its class. *Review Process*, *supra*.

After a drug is approved, the manufacturer must investigate and report adverse events to FDA. 21 C.F.R. 314.80. If such an event is serious and unexpected, the report must be made "as soon as possible but in no case later than 15 calendar days of initial receipt of the information by the applicant." 21 C.F.R. 314.80(c)(1)(i). Certain other information must be submitted to FDA within three working days. 21 C.F.R. 314.81(b)(1). A variety of other postmarketing reports are filed periodically, including quarterly and annual reports analyzing adverse events, 21 C.F.R. 314.80(c)(2), 314.81, and annual reports disclosing, among other things, all "significant new information * * * that might affect the safety, effectiveness, or labeling of the drug," including any new studies and data, 21 C.F.R. 314.81(b)(2)(i), (v), (vi). FDA also receives reports from health professionals and members of the public. FDA, *Postmarketing Surveillance Programs* (last modified Apr. 9, 2004) <http://www.fda.gov/cder/regulatory/applications/Postmarketing/surveillancepost.htm>.

Following its approval of a drug, FDA "monitors adverse events" from various reports, and "uses this information to update drug labeling." *Postmarketing Surveillance Programs*, *supra*. In addition, FDA "shall" withdraw its approval of an application if it finds, among other things, that the drug is not safe or effective under

the conditions of use specified in the drug's labeling. 21 U.S.C. 355(e).

2. In determining whether to grant or continue its approval of a new drug application, FDA does not merely impose minimum standards of safety, as the Vermont Supreme Court concluded. See Pet. App. 19a. "No drug is absolutely safe; all drugs have side effects." *Review Process, supra*; see *FDA* v. *Brown & Williamson Tobacco Corp.*, 529 U.S. 120, 142 (2000) ("[V]irtually every drug or device poses dangers under certain conditions."). Thus, FDA weighs health benefits against health risks. See 71 Fed. Reg. at 3934; 60 Fed. Reg. at 39,180; 47 Fed. Reg. 39,149 (1982). And FDA "generally considers a drug safe when the expected therapeutic gain justifies the risk entailed by its use." *United States* v. *Rutherford*, 442 U.S. 544, 555 (1979); accord *Brown & Williamson*, 529 U.S. at 140; *Review Process, supra*. The agency has, for example, approved cancer treatments that are highly toxic and thus not "safe" as that term is ordinarily used, but that are nonetheless safe in the relevant sense because the potential benefits to the health of cancer patients outweigh the risks. 61 Fed. Reg. 44,413 (1996); see *Brown & Williamson*, 529 U.S. at 142.

FDA's balancing of a drug's risks and benefits is similar to the balancing it undertakes in the analogous context of Class III medical devices. As this Court recently explained, FDA weighs the benefits of a Class III device against its risks, and FDA "may * * * approve devices that present great risks if they nonetheless offer great benefits in light of available alternatives." *Riegel*, 128 S. Ct. at 1004. So too with drugs. FDA's risk-benefit balancing looks in part to the availability of more effective or less risky alternatives. If similar, safer products

are already on the market, the agency may require a heightened health benefit to justify the heightened risk. For example, FDA determined in 2005 that a drug product called Bextra should be withdrawn from the market because it presented greater safety risks than other drugs for the same indication with comparable efficacy, and the manufacturer withdrew it. See FDA, *Alert for Healthcare Professionals, Valdecoxib (marketed as Bextra)* (Apr. 7, 2005) <http://www.fda.gov/cder/drug/InfoSheets/HCP/valdecoxibHCP.pdf>; Memorandum from John K. Jenkins & Paul J. Seligman through Steven Galson to NDA files 20-998, 21-156, 21-341, 21-042 at 17 (Apr. 6, 2005) <http://www.fda.gov/cder/drug/infopage/COX2/NSAIDdecisionMemo.pdf>. Similarly, FDA withdrew its approval of terfenadine when a safer alternative became available because the drug's risks no longer outweighed its benefits in light of the alternative. See 62 Fed. Reg. 1889 (1997); 63 Fed. Reg. 53,444 (1998). On the other hand, FDA decided *not* to withdraw its approval of erythromycin estolate despite the availability of alternatives with lower risks, because the drug's higher risks were "offset by" its greater efficacy in certain circumstances. 47 Fed. Reg. at 22,547-22,548.

3. In the course of weighing health risks and benefits, FDA considers the overall health consequences of including particular instructions or warnings in a drug's labeling. As explained above, a drug's safety and effectiveness are not determined in the abstract, divorced from its labeling. See 71 Fed. Reg. at 3934. Rather, FDA requires each new drug application to contain "a discussion of why the benefits exceed the risks *under the conditions stated in the labeling*." 21 C.F.R. 314.50(d)(5)(viii) (emphasis added); see 21 U.S.C. 355(d); 21 C.F.R. 314.50(c)(2)(ix). When FDA concludes that a

drug's benefits outweigh its risks only under certain conditions, the agency requires appropriate labeling to reflect that determination. See, *e.g.*, 21 C.F.R. 314.110(a).

Moreover, labeling must strike a balance between notifying users of potential dangers and not unnecessarily deterring beneficial uses through overwarning. 71 Fed. Reg. at 3935. "Exaggeration of risk could discourage appropriate use of a beneficial drug," and thereby harm the public health. *Ibid.* In addition, excessive warnings can cause more meaningful risk information to "lose its significance." 44 Fed. Reg. 37,447 (1979); accord 71 Fed. Reg. at 3935; 65 Fed. Reg. 81,083 (2000). "Warnings about dangers with less basis in science or fewer hazards could take attention away from those that present confirmed, higher risks." *Brooks* v. *Howmedica, Inc.*, 273 F.3d 785, 796 (8th Cir. 2001), cert. denied, 535 U.S. 1056 (2002). Thus, as the dissent in the Vermont Supreme Court explained, there are "a number of sound reasons why the FDA may prefer to limit warnings on product labels." Pet. App. 47a (quoting *Brooks*, 273 F.3d at 796).

B. FDA's Approval Of A Drug Preempts Claims Challenging The FDA-Approved Design Or Labeling When FDA Has Been Made Aware Of The Relevant Risk

Respondent's claims are preempted because they challenge labeling that FDA approved after being informed of the relevant risk.

1. When federal law merely seeks to impose minimum safety standards, state laws that impose more stringent safety standards ordinarily are not preempted because such standards do not ordinarily frustrate the federal government's objective to ensure minimum lev-

els of safety. See, *e.g.*, *Sprietsma* v. *Mercury Marine*, 537 U.S. 51, 57 n.6, 64-68 (2002); cf. *Lohr*, 518 U.S. at 501 (emphasizing, in holding that FDA's substantial-equivalence determination for a grandfathered medical device did not expressly preempt state tort claims, that FDA had *not* "weighed the competing interests relevant to the particular requirement in question").

Where, however, federal regulation is designed to strike a *balance* between competing considerations, state laws that strike a different balance are impliedly preempted because they interfere with the federal balancing. *Bonito Boats, Inc.* v. *Thunder Craft Boats, Inc.*, 489 U.S. 141, 152 (1989); *Chicago & N.W. Transp. Co.* v. *Kalo Brick & Tile Co.*, 450 U.S. 311, 321, 326-327, 330 (1981). In *Geier*, for example, an agency did not merely impose minimum safety standards. 529 U.S. at 874-875. Instead, it determined that, in light of competing considerations, public safety was best served by affording manufacturers the choice to install a variety of different passive restraint systems in their vehicles. *Id.* at 881. The Court held that a state suit seeking to impose liability for a manufacturer's decision not to use a particular type of restraint system would stand as an obstacle to the federal agency's decision. *Id.* at 881-883; see also, *e.g.*, *Buckman Co.* v. *Plaintiffs' Legal Comm.*, 531 U.S. 341, 348 (2001) (fraud-on-FDA claim preempted because it would interfere with FDA's ability to strike "a somewhat delicate balance of statutory objectives"); *International Paper Co.* v. *Ouellette*, 479 U.S. 481, 494 (1987) (state nuisance law preempted because it would "upset[] the balance of public and private interests so carefully addressed by" the federal permitting regime for water pollution).

2. So too here, the jury's imposition of liability based on petitioner's use of FDA-approved labeling would interfere with FDA's expert weighing of risks and benefits. As discussed above, FDA approves labeling for a new drug based on its determination that the labeling strikes the appropriate balance between health risks and benefits. See pp. 16-17, *supra*. Overwarning can both deter beneficial uses of a drug and "limit physician appreciation of potentially far more significant" risks. 71 Fed. Reg. at 3935; see 65 Fed. Reg. at 81,083. Accordingly, FDA's approval of a new drug under the FDCA and its implementing regulations "establish[es] both a 'floor' and a 'ceiling'" with respect to drug labeling. 71 Fed. Reg. at 3935.

That conclusion is confirmed by the fact that liability under state law turns on whether a drug, as labeled, is "unreasonably dangerous." Pet. App. 35a (Rieber, C.J., dissenting) (quoting *Town of Bridport* v. *Sterling Clark Lurton Corp.*, 693 A.2d 701, 704 (Vt. 1997)); J.A. 15 (respondent's complaint); J.A. 219 (jury instructions). Any such finding would directly conflict with FDA's determination that the drug *is* safe and effective under the conditions prescribed, recommended, or suggested in the labeling. Pet. App. 35a-36a. Indeed, respondent specifically urged the jury to second-guess FDA and reject the agency's expert judgment. See J.A. 82, 85, 98, 211, 212, 249.

If a state regulatory agency directed manufacturers not to use FDA-approved labeling, but instead to provide different or additional warnings, the conflict with federal law would be manifest. As in *Riegel*, the conflict is exacerbated, rather than ameliorated, by the fact that juries would make those determinations in individual tort suits. As the *Riegel* Court explained, a jury tends

to focus on the risk of a particular design or labeling that arguably contributed to a particular plaintiff's injury, not on the overall benefits of that design or labeling; "the patients who reaped those benefits are not represented in court." 128 S. Ct. at 1008. In contrast, FDA's drug-approval determinations consider the interests of *all* potential users of a drug, including "those who would suffer without new medical [products]" if juries in all 50 States were free to second-guess FDA's expert determinations. *Id.* at 1009; see Pet. App. 48a (Reiber, C.J., dissenting).

Thus, just as "[s]tate tort law that requires a manufacturer's [Class III medical devices] to be safer, but hence less effective, than the model FDA has approved disrupts the federal scheme," *Riegel*, 128 S. Ct. at 1008, state tort law that requires a manufacturer to use different labeling than that approved by FDA would disrupt the federal balance.

Here, there is no question that FDA was presented with extensive information about the dangers of accidental intra-arterial injection from intravenous administration of the drug. Indeed, the agency approved labeling that explained how to inject the drug intravenously so as "to avoid * * * inadvertent intra-arterial injection," and thereby ensured that the drug was safe and effective under the stated conditions of use. Pet. App. 167a; see pp. 4-5, *supra*. Nor did the Vermont Supreme Court point to any marked change in the number or type of reported cases of accidental intra-arterial injection from intravenous administration establishing that the risk was of a distinct type or substantially greater magnitude than the risks of which FDA had been made aware. Thus, the state supreme court's decision sanctioned

what amounts to a frontal assault on FDA's approval of the labeling in question.

C. Federal Law Does Not Permit Manufacturers To Make Unilateral Changes To FDA-Approved Labeling Based On Previously Available Information

In holding that respondent's claims are not preempted, the Vermont Supreme Court relied in large part on its view that an FDA regulation, 21 C.F.R. 314.70(c), "allow[s] unilateral changes to drug labels whenever the manufacturer believes it will make the product safer." Pet. App. 13a. That is incorrect. Petitioner was not free to disregard FDA's judgment concerning previously known risks.

1. As discussed above, the FDCA requires a manufacturer to receive FDA's approval for a new drug's labeling. 21 U.S.C. 355(a) and (d). Because FDA's approval strikes an important balance between, among other things, warning of risks and not overdeterring beneficial uses, manufacturers ordinarily may *not* modify designs or labeling approved by FDA without first obtaining FDA's approval for the change. See 21 C.F.R. 314.70; cf. *Riegel*, 128 S. Ct. at 1005, 1007 (discussing similar requirement for Class III devices). Here, for example, FDA instructed petitioner that the "final printed labeling * * * must be identical" to the approved labeling. Pet. App. 165a. Indeed, a unilateral modification of the labeling, absent special circumstances, can open a manufacturer to liability for misbranding the drug. See 21 U.S.C. 352(a); 21 U.S.C. 352(f) (Supp. V 2005); 21 C.F.R. 201.100(c)(1) and (d); see also 21 U.S.C. 355(a). If manufacturers were free to make unilateral changes to labeling the day after FDA's approval based on information that was previously available to

the agency, the approval process would be greatly undermined and the agency's careful balancing of risks and benefits thwarted. The Vermont Supreme Court's view that "FDA approval of a drug label" is nothing more than "a first step," *id.* at 15a, is therefore a fundamental misconception of the federal regulatory framework.

Under FDA's regulations, a manufacturer ordinarily must submit a supplemental application before making any changes to an approved drug, including changes in labeling. 21 C.F.R. 314.70(b)(2)(v). As a general rule, the manufacturer must obtain prior approval by FDA before making such changes. Section 314.70(c)(6), on which the court below relied, provides only a *limited* exception to that rule permitting "the holder of an approved [new drug] application [to] commence distribution of the [changed] drug product involved upon receipt by the agency of a supplement for the change" if, among other requirements, the change "add[s] or strengthen[s]" a warning or a statement about administration of the drug in order to promote safety. 21 C.F.R. 314.70(c)(6)(iii)(A) and (C). And even that limited exception requires submission of a supplemental new drug application to, albeit not prior approval by, the agency.

As FDA explained when it proposed that regulation in 1982, however, substantive changes may be made without prior FDA approval only "to correct concerns about *newly discovered* risks from the use of the drug." 47 Fed. Reg. at 46,623 (emphasis added). FDA determined that, "[a]lthough most changes in labeling would require the applicant to submit a supplement and obtain FDA approval before making a change," some changes that "would make available *important new information* about the safe use of a drug product" could be made upon submission of a supplemental application. *Id.* at

46,635 (emphasis added); see also FDA, *Guidance for Industry, Changes to an Approved NDA or ANDA* 25 (Nov. 1999) <http://www.fda.gov/cder/guidance/2766fnl.pdf> (explaining that changes may be made without prior FDA approval to add "a precaution arising out of a *postmarketing* study") (emphasis added).

In a proposed rule issued in January 2008, FDA confirmed that interpretation of Section 314.70(c). 73 Fed. Reg. 2848 (2008). The proposed rule would "reaffirm [FDA's] longstanding position that a supplemental application * * * is appropriate to amend the labeling for an approved product *only to reflect newly acquired information*," and may "add or strengthen a contraindication, warning, precaution, or adverse reaction only if there is sufficient evidence of a causal association with the drug, biologic, or device." *Ibid.* (emphasis added). FDA explained that "[a]llowing sponsors to unilaterally amend the labeling for approved products without limitation—even if done to add new warnings—would undermine the FDA approval process required by Congress" and "disrupt FDA's careful balancing of how the risks and benefits of the product should be communicated." *Id.* at 2849. Thus, the supplemental-application process is "primarily designed to provide information to FDA so that the agency," not the manufacturer, "can decide when safety information should be included in the labeling for a product." *Ibid.*

Even when a manufacturer may make a change prior to FDA's approval under Section 314.70(c), the supplemental application must "give a full explanation of the basis for the change." 21 C.F.R. 314.70(c)(3). The agency may then reject the change based on its own balancing of the relevant health risks and benefits. See 21 C.F.R. 314.70(c)(7). If FDA rejects the change, it may

order the manufacturer to cease further distribution of the changed product. *Ibid.* Thus, whether to authorize a change remains "squarely and solely FDA's" decision. 71 Fed. Reg. at 3934. Moreover, products distributed with a unilaterally changed label "remain[] subject to enforcement action" if FDA finds that the unilateral change rendered "the labeling false or misleading." *Ibid.*; see 21 U.S.C. 352 (2000 & Supp. V 2005). In practice, therefore, manufacturers typically consult with FDA before making any labeling changes. See 73 Fed. Reg. at 2849; 71 Fed. Reg. at 3934.

As the dissent in the Vermont Supreme Court correctly explained, Section 314.70(c) does not "allow manufacturers to simply reassess and draw different conclusions regarding the same risks and benefits already balanced by the FDA." Pet. App. 40a. Instead, any changes to a drug's labeling without prior FDA approval must be the subject of a supplemental application, which FDA can approve or reject, and must be based on new information establishing that risks arising from use of the drug are of a different type or greater severity than the risks of which FDA had previously been made aware—not cumulative new information that does not add to the information that was previously available to the agency. FDA's interpretation of its own regulation is entitled to significant deference. See, *e.g.*, *Auer* v. *Robbins*, 519 U.S. 452, 461 (1997).

For that reason, a state law premising liability on petitioner's failure to depart from the FDA-approved labeling concerning intravenous injection of the drug would not only "stand[] as an obstacle to the accomplishment and execution of the full purposes and objectives of Congress," *Hines*, 312 U.S. at 67, it would also "make it 'impossible' for private parties to comply with both

state and federal law," *Geier*, 529 U.S. at 873. See 73 Fed. Reg. at 2853. Under respondent's theory, petitioner would have had to change the FDA-approved labeling, but petitioner could not have done so without prior FDA approval.

2. The parties have disputed whether FDA expressly rejected the precise warning that respondent asserts should have been included in the labeling. See, *e.g.*, Br. in Opp. 15-17. That factual dispute is irrelevant, because it is FDA's approval decision—which, in this case, followed the disclosure of the relevant risk—not the specifics of the agency's deliberations or speculation about whether the agency might have modified the label in some manner not expressly proposed at the time of the approval, that gives rise to preemption. Any state-law liability would be premised on a re-weighing of the same risks and benefits that FDA already considered in deciding to approve the precise labeling at issue, and federal law would preclude the applicant from making the state-mandated change without prior FDA approval. The agency could not reasonably be expected to *expressly* reject every possible variant of approved labeling as part of its decisional process. Indeed, it would underestimate the post hoc imagination of lawyers to think such an exhaustion of potential variants by the manufacturer or the agency is even possible. More to the point, such express rejection of a precise proposal is not necessary for preemption.

Moreover, any inquiry into the specifics of FDA's decisionmaking process would pose serious practical concerns. Here, FDA expressly rejected one particular labeling change proposed by petitioner, see Pet. App. 17a-18a, but it appears that FDA viewed the change as non-substantive and rejected it for formatting reasons,

cf. *id.* at 18a. With the passage of time, however, it would be increasingly difficult to reconstruct the agency's decisionmaking process. If preemption turned on the details of the agency's deliberations, preemption analysis would devolve into an intrusive, and potentially inconclusive, second-guessing of the agency's decisional process. Such an intrusion could also impose unreasonable discovery demands on the agency to explain the details of its deliberative process. Cf. U.S. Br. at 21-23, *Warner-Lambert* v. *Kent*, 128 S. Ct. 1168 (2008); U.S. Br. at 28-30, *Buckman*, *supra*.

3. As in *Riegel*, this Court need not rely on deference to FDA's views to conclude that respondent's claims challenging FDA's weighing of health risks and benefits are preempted. See *Riegel*, 128 S. Ct. at 1009. But FDA's interpretation of its own regulations is entitled to significant deference. See *Auer*, 519 U.S. at 461. And FDA's further views on preemption are also entitled to some weight under *Skidmore* v. *Swift & Co.*, 323 U.S. 134 (1944). Cf. *Riegel*, 128 S. Ct. at 1009. FDA's role in administering its own drug approval process makes it "uniquely qualified to determine whether a particular form of state law 'stands as an obstacle to the accomplishment and execution of the full purposes and objectives of Congress.'" *Lohr*, 518 U.S. at 495-496 (quoting *Hines*, 312 U.S. at 67); see *Geier*, 529 U.S. at 883 (explaining that an agency has a "thorough understanding of its own regulation and its objectives and is 'uniquely qualified' to comprehend the likely impact of state requirements") (quoting *Lohr*, 518 U.S. at 496).

In the preamble to a January 2006 rule concerning the labeling of drugs, FDA explained that the government's "long standing view[ ]" is that "FDA approval of labeling under the [FDCA] * * * preempts conflicting

or contrary State law," especially considering that "FDA interprets the [FDCA] to establish both a 'floor' and a 'ceiling'" for labeling. 71 Fed. Reg. at 3934, 3935. The agency also "recognize[d] that FDA's regulation of drug labeling will not preempt all State law actions." *Id.* at 3936. FDA then provided some specific examples of circumstances in which state laws are preempted, though it did not attempt to exhaust such circumstances. See *id.* at 3935-3936 (noting that "at least" those examples would be preempted). In this brief, the government has articulated a more generally applicable rule of decision, consistent with those examples, based on the preamble's explanation that (i) the labeling requirements are not a mere minimum safety standard, but rather strike a balance between risks and benefits, and (ii) FDA's regulations permit changes in labeling without prior approval only in narrow circumstances. See *id.* at 3934-3935; see also 73 Fed. Reg. at 2853; *Testimony of Deputy FDA Commissioner Randall Lutter Before The House Comm. on Oversight and Government Reform* 1-2 (May 14, 2008) <http://oversight.house.gov/documents/20080514142253.pdf>.[2]

Respondent suggests (Supp. Pet. Stage Br. 2 n.1; Br. in Opp. 19 n.6) that the government took a different position in a district court filing in *Perry* v. *Novartis*, Civ. No. 05-5350 (E.D. Pa. Sept. 21, 2005). The *Perry* brief

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[2] Respondent's reliance (Br. in Opp. 8, 28) on snippets from various earlier Federal Register notices is misplaced because those notices did not squarely address the preemption question here. See 65 Fed. Reg. at 81,103 (stating that proposed *changes* to existing labeling rules would not have federalism implications); 63 Fed. Reg. at 66,384 (response to comments concerning Medication Guides for "a small number of products," *id.* at 66,379); 44 Fed. Reg. at 37,437 (responding to comment that FDA should use different administrative procedures).

argued, however, that failure-to-warn claims "premised on scientific information known to and considered by FDA as part of the approval process, would * * * be preempted." U.S. Br. at 12, *Perry*, *supra*. Respondent quotes (Br. in Opp. 19 n.6) a portion of the brief stating that FDA approval does not preempt *all* state-law labeling claims, because manufacturers may make labeling changes without prior FDA approval in some circumstances. The brief went on to explain, however, that such changes may "be made to warn of *new* hazards or cautions." U.S. Br. at 11, *Perry*, *supra* (emphasis added). Thus, the *Perry* brief is one of several amicus filings in which the government addressed FDCA preemption issues on a more fact-specific basis, without articulating a more general rule of decision.

D. Neither The 1962 Nor The 2007 Amendments To The FDCA Displaced The Operation Of Ordinary Conflict-Preemption Principles

1. The Vermont Supreme Court mistakenly thought that Section 202 of the 1962 amendments to the FDCA precludes the application of ordinary preemption principles. See Pet. App. 21a-23a. That provision states as follows:

> Nothing in the amendments made by this Act to the Federal Food, Drug, and Cosmetic Act shall be construed as invalidating any provision of State law * * * unless there is a direct and positive conflict between such amendments and such provision of State law.

76 Stat. 793.

At the outset, it is not clear to what extent Section 202 applies here. It is limited to "the amendments made by" the 1962 legislation. § 202, 76 Stat. 793. While those

amendments broadened the scope of FDA's new drug approval process by requiring the agency to consider the efficacy as well as the safety of a drug, see § 102(b), 76 Stat. 781, FDA's new drug approval process predated the amendments, see 21 U.S.C. 355(a) and (d) (1958). Indeed, FDA approved Phenergan before 1962. See Pet. 6; Br. in Opp. 23 n.8.

Assuming *arguendo* that Section 202 is relevant in this case, that provision means only that the 1962 amendments do not preempt *the field* of drug regulation; it does not manifest an intent to displace ordinary principles of conflict preemption. 71 Fed. Reg. at 3935 n.8. To the contrary, Section 202 expressly contemplates preemption in circumstances involving "a direct and positive conflict." 76 Stat. 793. The Vermont Supreme Court read that phrase to refer only to situations in which it would be impossible to comply with both federal and state law, as distinguished from situations in which state law would frustrate the purpose of the federal scheme. Pet. App. 21a-23a. Any such distinction is irrelevant here because, as discussed above, the impossibility standard is satisfied in this case. See pp. 21-25, *supra*.

In any event, at the time of the 1962 amendments, the phrase "direct and positive conflict" had long been understood to refer to conflict preemption generally, not to a mere subset of such preemption. See, *e.g.*, *United Constr. Workers* v. *Laburnum Constr. Corp.*, 347 U.S. 656, 663 n.5 (1954); *Sinnot* v. *Davenport*, 63 U.S. (22 How.) 227, 243 (1859). This Court has long contrasted "direct and positive" conflict preemption with "field" preemption, rather than using it as a byword for the impossibility variant of conflict preemption. *E.g.*, *Kelly* v. *Washington ex rel. Foss Co.*, 302 U.S. 1, 9-10 (1937).

Indeed, the Court found a "direct and positive conflict" in circumstances analogous to this one, where federal law imposed some conditions and state law purported to impose an *additional* one that would frustrate Congress's objective. *Sinnot*, 63 U.S. (22 How.) at 241-243. More generally, this Court has never "driven a legal wedge—only a terminological one—between 'conflicts' that prevent or frustrate the accomplishment of a federal objective and 'conflicts' that make it 'impossible' for private parties to comply with both state and federal law." *Geier*, 529 U.S. at 873. A sponsor of Section 202 confirmed that the phrase "direct and positive conflict" takes its ordinary meaning by explaining that the amendment "would merely say that this Food and Drug Act shall not be construed as the intent of Congress to abolish *all* State laws on the same subject *where they are not in conflict with the Federal law.*" 108 Cong. Rec. 21,083 (1962) (emphases added).

Not surprisingly then, "[t]he Court has * * * refused to read general 'saving' provisions to tolerate actual conflict both in cases involving impossibility *and* in 'frustration-of-purpose' cases." *Geier*, 529 U.S. at 873-874 (citation omitted). Especially considering that the Constitution itself, via the Supremacy Clause (U.S. Const. Art. VI, Cl. 2), subordinates state law to federal law, the courts should not lightly assume that federal law is so self-negating as to authorize state law to frustrate its objectives. Thus, even when a statute contained a savings clause providing that "[c]ompliance with" a federal safety standard "does not exempt any person from any liability under common law," 15 U.S.C. 1397(k) (1988), this Court held that the clause did not preclude the application of ordinary conflict preemption principles, including frustration-of-purpose principles. *Geier*,

529 U.S. at 868, 873-874. The savings clause here, which expressly provides for conflict preemption, likewise does not displace ordinary conflict preemption principles.

Nor is it material that the FDCA lacks an express preemption provision for drugs like the one at issue in *Riegel*. When Congress enacted a premarket approval process for Class III medical devices in 1976, it expressly preempted state requirements that are "different from, or in addition to," certain federal requirements (21 U.S.C. 360k(a); see *Riegel*, 128 S. Ct. at 1003)—*i.e.*, state-law provisions that conflict most directly with the federal regime. The enactment of that provision in 1976 does not suggest that FDA's new drug approval process has any less preemptive effect, because the device amendments were enacted years later by a subsequent Congress. See *Gomez-Perez* v. *Potter*, No. 06-1321, slip op. 10 (May 27, 2008); *California Div. of Labor Standards Enforcement* v. *Dillingham Constr., N.A., Inc.*, 519 U.S. 316, 331 n.8 (1997). Rather, the presence of an express preemption provision for devices but not drugs is explained by the fact that Congress legislated in 1976 against the backdrop of a then-existing state premarket approval requirement for devices, whereas States do not appear to have had similar requirements for drugs in 1938, when the FDCA was enacted. See *Riegel*, 128 S. Ct. at 1017-1018 (Ginsburg, J., dissenting); see also H.R. Rep. No. 853, 94th Cong., 2d Sess. 45 (1976). Moreover, this Court has looked to conflict preemption principles in determining whether a federal requirement applicable to a device is different from, or in addition to, a state requirement, and thus expressly preempted by Section 360k(a). See *Riegel*, 128 S. Ct. at 1008; *Lohr*, 518 U.S. at 500; *id.* at 508 (Breyer, J., concurring in part and in the judgment).

2. Respondent has suggested (Supp. Pet. Stage Br. 8-9) that recent amendments to the FDCA bear on the question presented. But those amendments do not reflect any intent to limit the FDCA's preemptive effect. In 2007, Congress enacted Section 901(a) of the FDAAA, Pub. L. No. 110-85, 121 Stat. 922, to enhance FDA's authority to require applicants to undertake postmarketing actions, including additional clinical studies, clinical trials, and safety labeling changes. That provision specifies that it "shall not be construed to affect the responsibility of the responsible person or the holder of the approved application * * * to maintain its label in accordance with existing requirements, including subpart B of part 201 and sections 314.70 and 601.12 of title 21, Code of Federal Regulations (or any successor regulations)." 121 Stat. 925-926 (to be codified at 21 U.S.C. 355(o)(4)(I) (Supp. I 2007)). That simply means that the relevant amendments do not affect obligations under other *federal* laws. It does not manifest any intent to depart from the application of ordinary principles governing the preemption of conflicting *state* laws.

Respondent selectively quotes floor statements of some individual legislators suggesting that, in their view, the FDCA does not preempt state-law claims. Supp. Pet. Stage Br. 8-9. At least as many other legislators, however, opined that the FDCA would continue to have broad preemptive effect. See, *e.g.*, 153 Cong. Rec. S11,940 (daily ed. Sept. 21, 2007) (Sen. Gregg); *id.* at S11,839-S11,840 (Sen. Coburn); *id.* at S11,939 (Sen. Enzi); *id.* at S12,050 (daily ed. Sept. 25, 2007) (Sen. Alexander). And as noted, the text of the rule of construction that Congress actually enacted, which is limited to the effect of Section 901, itself preserves *complemen-*

tary federal requirements without evincing any intent to protect *conflicting state* laws.

CONCLUSION

The judgment of the Supreme Court of Vermont should be reversed and the case remanded for further proceedings.

Respectfully submitted.

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IN THE
SUPREME COURT OF THE UNITED STATES

WYETH,
Petitioner,

v.

DIANA LEVINE,
Respondent.

ON WRIT OF CERTIORARI TO
THE VERMONT SUPREME COURT

BRIEF *OF AMICI CURIAE* AARP, THE NATIONAL WOMEN'S HEALTH NETWORK, AND PRESCRIPTION ACCESS LITIGATION IN SUPPORT OF RESPONDENT

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STATEMENT OF INTEREST OF *AMICI CURIAE* [1]

AARP is a nonpartisan, nonprofit organization with nearly forty million members, including members in each of the fifty states and the District of Columbia. AARP works to foster the health and economic security of individuals as they age. To that end, AARP supports efforts at state and national levels to ensure access to safe and effective health care services and products. AARP is greatly concerned about the safety of prescription drugs because older people disproportionately use them compared to their younger counterparts. AARP supports laws and public policies designed to protect its members' rights and to preserve the availability of legal redress when its members are harmed in the marketplace.

The National Women's Health Network (NWHN) is a nonprofit, nonpartisan organization with thousands of members nationwide that improves the health of all women by influencing policy and supporting informed consumer decision-making. The NWHN has a significant interest in protecting the health of women, who use the health care system more frequently than men, from injuries due to untested, unsafe and misbranded drugs. The NWHN believes

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[1] This brief is being submitted with the consent of the parties. It was prepared on behalf of AARP, the National Women's Health Network, and Prescription Access Litigation by their undersigned counsel. It was not authored, in whole or in part, by counsel for any party. No person or entity other than AARP, the National Women's Health Network, and Prescription Access Litigation or their counsel made a monetary contribution to the preparation or submission of the brief.

that effective state tort law remedies are necessary to protect women from unsafe drugs.

The Prescription Access Litigation Project (PAL), a project of the nonpartisan nonprofit organization Community Catalyst, uses litigation and consumer education to challenge illegal pharmaceutical industry tactics. PAL is a coalition of over 130 state, local, and national organizations, including senior citizen groups, consumer advocates, health care advocates, legal services offices, nonprofit health plans, labor unions, and union benefit funds. The members of the PAL coalition have a combined membership of over 13 million individuals. A number of PAL member organizations are plaintiffs in lawsuits regarding drug marketing and advertising that involve preemption issues under the Federal Food, Drug, and Cosmetic Act.

Amici have a significant interest in this case. The issue before the Court could directly affect the ability of each organizations' members to seek redress when injured by dangerous pharmaceutical products that lack appropriate warnings about the risks of using those products. In addition, the Court's resolution of the preemption question in this case could have a broad impact on public safety regarding the use of prescription drugs. Petitioner seeks to eliminate the traditional role played by the tort system and leave the Food and Drug Administration ("FDA") as the sole protector of the American public with regard to drug safety. Yet the FDA lacks the resources, independence, and regulatory authority to perform this task on its own. As such, the practical

reality is that Petitioner's approach would sharply increase the public's risk of injury from inadequately labeled drugs. *Amici* have a strong interest in preventing this outcome, and can offer a different perspective on the issues before the Court than those of the parties.

Amici believe that the tort system should remain vibrant even if the FDA becomes more effective at promoting drug safety, and that partnership between a vibrant tort system and an effective regulatory agency will best protect the American public from inadequately labeled drugs. *Amici* fully support the arguments made by the Respondent and supporting *amici curiae* on these points. In order to prevent duplication of argument, however, this brief focuses solely on the FDA's shortcomings as the sole guarantor of public safety with respect to drug products.

SUMMARY OF ARGUMENT

The Petitioner argues the FDA possesses exclusive authority to protect the American public from unsafe drugs and to assure that prescription drugs are properly labeled. This position faces serious practical problems. First, the FDA simply does not have the resources to monitor effectively the performance of every marketed drug and to ensure that every drug's label adequately warns of the drug's risks. The FDA's lack of resources to protect the public from unsafe or inadequately labeled drugs has been noted by sources both within and without the agency, including the General Accounting Office, the Institute

of Medicine, and the FDA's own Science Board. These sources have emphasized the agency's inability to monitor the safety of drugs once they are on the market, and they have concluded that the FDA's ineffectiveness places American lives at risk. As one FDA employee bluntly stated, "the FDA and its Center for Drug Evaluation and Research are broken." *See* Testimony of David Graham before the U.S. Senate Finance Committee (Nov. 18, 2004) at 4 ("Graham Testimony"), available at http://finance.senate.gov/hearings/testimony/2004test/111804dgtest.pdf.

The FDA's capacity to ensure drug safety is limited not only by lack of resources, but also by its lack of independence from the pharmaceutical industry. Because the FDA does not have the capacity to conduct independent research regarding drug safety, it relies entirely on the pharmaceutical industry to perform the needed clinical research and provide the FDA with the results. The FDA then relies heavily on industry financing and personnel to support its review of industry-provided data. Numerous FDA scientists also have stated that commercial interests inappropriately influence FDA decisions regarding drug products, revealing yet another limitation on the FDA's ability to protect the public from unsafe or inadequately labeled drugs.

Finally, resource constraints aside, the FDA lacks effective regulatory authority to require manufacturers to strengthen warning labels to reflect newly-discovered risks. The FDA enjoyed no direct power to impose a post-approval labeling change until passage of the Food and Drug Amendments Act of

2007, Pub. L. No. 110-85, 121 Stat. 823 (the "FDAAA"). The FDAAA provides the FDA with some power in this regard, but the statute limits that power by requiring the FDA to undertake extensive negotiations with a drug's sponsor and by providing the FDA with no right of unilateral action. *See* 21 U.S.C. § 355(o). The authority provided by the FDAAA is further limited by the FDA's lack of resources, which disables the FDA from acting effectively across the full range of post-marketing safety issues.

Because of these practical limitations, the FDA is unable to assume sole responsibility for protecting the American public from inadequately labeled drugs. The Court should reject the Petitioner's approach, and preserve the historic relationship between the tort system and the FDA with regard to ensuring that drugs are safe and properly labeled.

ARGUMENT

I. The FDA lacks the resources to ensure drug safety.

The pro-preemption position advanced by the Petitioner and its *amici* faces a serious practical problem: it is based on an unrealistic assessment of the FDA's actual ability to detect the unforeseen adverse effects of an approved drug and to take appropriate remedial action. As a former FDA Commissioner recently wrote, "[t]he reality is that the FDA does not have the resources to perform the Herculean task of monitoring comprehensively the performance of every drug on the market." David A.

Kessler and David C. Vladeck, *A Critical Examination of the FDA's Efforts to Preempt Failure-to-Warn Claims*, 96 Geo. L.J. 461, 484-85 (2008).

The FDA's practical ability to monitor the performance of marketed drugs is of immense public health importance, especially because of the limited information available to the agency before approval about a new drug's risks and potential adverse effects. Pre-approval clinical studies of a new drug typically involve carefully controlled study conditions and at most a few thousand subjects who do not represent the full array of patients who will use the drug when it is placed on the market. *See id.* at 466. Often, only after a drug enters the marketplace do the drug's full range of risks become apparent, including risks that are rare, affect specific sub-populations, or manifest themselves only over long periods of time. *See id.* The FDA simply lacks sufficient resources to keep pace with this emerging information and to take effective remedial action when a drug proves to be inadequately labeled, as set forth further below.

The FDA unit tasked with reviewing and monitoring pharmaceutical products is the Center for Drug Evaluation and Research ("CDER"). This unit has limited personnel and funding for post-marketing drug safety. With regard to personnel, CDER's Office of Drug Safety ("ODS") employs only 100 people to monitor post-marketing drug safety for over 11,000 FDA-approved drugs, including over 3,000 prescription drugs, in a country whose doctors write in excess of 3.3 billion prescriptions per year. *See id.*; FDA Science Mission at Risk, Report of the Subcommittee on

Science and Technology at 11 (Nov. 2007) (the "FDA Science Board Report"), available at http://www.fda.gov/ohrms/dockets/AC/07/briefing/2007-4329b_02_01_FDA%20Report%20on%20Science%20and%20Technology.pdf. In contrast, reflecting the FDA's prioritization of the drug approval process, approximately ten times as many employees work in CDER's Office of New Drugs ("OND"), which primarily reviews applications for new drugs and approves approximately 100 new drugs each year. *See* Kessler and Vladeck, 96 Geo. L.J. at 485; United States Government Accountability Office, *Report to Congressional Requesters: Drug Safety – Improvement Needed in FDA's Post-Market Decision-Making and Oversight Process* at 14 (March 2006) (the "GAO Report").

The financial resources devoted to monitoring the safety of marketed drugs are similarly weak, partly because of the Prescription Drug User Fee Act of 1992 ("PDUFA"), Pub. L. No. 102-571, 106 Stat. 4491. PDUFA was enacted to accelerate the review of new drug applications. It placed strict timelines on the review process in exchange for user fees from the companies seeking the FDA's approval of new drugs. Although PDUFA successfully decreased the FDA's review times for new drugs, its initial versions prohibited the use of fees for any post-marketing drug safety activities. Congress eased restrictions on the FDA's use of PDUFA funds when reauthorizing the statute in 2002, but the resource disparity remains: ODS had 2005 expenditures of only $26.9 million, whereas OND had 2005 expenditures of $110.6

million, more than four times as much. *See* GAO Report at 8.

Thus, the FDA has barely 100 employees to monitor the post-approval performance of 11,000 drugs (over 100 drugs per employee), and those employees are supported by funding levels less than one quarter of the amount devoted to new drug approval. Given this data, it is not surprising that FDA's own employees have questioned the agency's ability to ensure the safety of prescription drugs on the market. In 2004, FDA Drug Safety Officer David Graham, M.D., M.P.H., gave congressional testimony placing the FDA's ineffective response to reports of increased cardiac adverse events among Vioxx users into a broad context:

> Vioxx is a terrible tragedy and a profound regulatory failure. I would argue that the FDA, as currently configured, is incapable of protecting America against another Vioxx. We are virtually defenseless. It is important that this Committee and the American people understand that what happened with Vioxx is really a symptom of something far more dangerous to the safety of the American people. Simply put, the FDA and its Center for Drug Evaluation and Research are broken.

See Graham Testimony at 4 (emphasis added). Dr. Graham's concern that the FDA is "broken" regarding post-marketing drug safety is widely shared by the

FDA's professional staff. In 2006, the Union of Concerned Scientists ("UCS") polled FDA scientists on a range of issues. The poll found that 66% of respondents were "not at all confident" or only "somewhat confident" that the FDA adequately monitored the safety of prescription drugs after they reached the market. *See* UCS 2006 Food and Drug Administration Survey ("UCS Survey"), available at www.ucsusa.org/assets/documents/scientific_integrity/Additional-Questions-and-Responses.pdf. The poll also found that 42% of the survey respondents were "not at all confident" or only "somewhat confident" that the FDA's final decisions adequately assessed drug safety. *See id.*

Independent evaluators have reached similar conclusions. In March 2006, the GAO reported to Congress on the FDA's oversight of drug safety. *See* GAO Report, *supra*. There, the GAO sharply criticized the FDA's ability to respond effectively to post-marketing safety issues:

> The FDA lacks clear and effective processes for making decisions about, and providing management oversight of, postmarket safety issues. The process is limited by a lack of clarity about how decisions are made and about organizational roles, insufficient oversight by management, and data constraints. [GAO] observed a lack of criteria for determining what safety actions to take and when to take them.

....

> Some of FDA's initiatives, such as the establishment of a Drug Safety Oversight Board (DSB), a draft policy on major postmarket drug safety decision making, and the identification of new data sources, may improve the postmarket drug safety decision-making process, but they will not address all the gaps we identified.

Id. at 5.

The Institute of Medicine ("IOM"), a non-profit society chartered by Congress to advise the federal government on scientific and technical matters, also has identified serious problems with the FDA's oversight of drug safety. In 2004, the FDA contracted with IOM to examine its regulation of drug safety in light of public health failures (such as Vioxx) that called into question FDA's capacity to evaluate drug safety. IOM published a massive study in September 2006 that highlighted the FDA's lack of resources as an impediment to the FDA's ability to act effectively:

> The [FDA] lacks the resources needed to accomplish its large and complex mission today, let alone to position itself for an increasingly challenging future. Despite the fact that so much has changed in drug discovery and development, in the number and complexity of FDA's Congressionally mandated

> responsibilities, in the practice of medicine, the structuring and delivery of health care, the way drugs are used, the role of patients and consumers, and the information environment, FDA appropriations for new drug reviews have remained roughly flat (in constant dollars) since the passing of the Prescription Drug User Fee Act (PDUFA) (GAO, 2002; Thompson, 2000). User-fees have led to an overall increase in resources for new drug review, but activities not funded by user fees have received a smaller portion of FDA's total budget. There is little dispute that FDA in general is, and CDER specifically remains, severely underfunded (Goldhammer A, 2005; Wolfe S, 2006).

Institute of Medicine of the National Academies, *The Future of Drug Safety: Promoting and Protecting the Health of the Public* at 7-1 (Alina Baciu, Kathleen Stratton and Sheila P. Burke, eds., 2006) ("IOM Report").

The IOM Report specifically expressed concern about the inadequate funding for post-marketing drug safety:

> There is widespread agreement that resources for postmarketing drug safety work are especially inadequate and that resource limitations have hobbled the agency's ability to improve and expand

> this essential component of its mission. Continued resource shortages will impede the agency's ability to use new and future scientific and technological advances in drug research across the lifecycle. In particular, the limited resources could impede the agency's ability to detect risks of new drugs in a timely fashion, analyze emerging drug safety data, and effectively communicate that information to the public in the ways envisioned in the committee's report.

Id.

Many of the FDA's own doctors and scientists share the IOM's concern. Seventy percent of respondents to the 2006 UCS Survey mentioned above stated that the FDA lacks sufficient resources to protect public health, and two-thirds of respondents worried that the FDA cannot adequately monitor the safety of drugs once they are on the market. *See* UCS Survey, *supra*. This level of concern is long-standing: approximately the same percentage of FDA doctors and scientists expressed such views in response to a 2003 poll conducted by the Office of the Inspector General of the Department of Health and Human Services. *See* Office of the Inspector General, Department of Health and Human Services, *FDA's Review Process for New Drug Applications: A Management Review* at 12, 19 (2003), available at http://www.fda.gov/ola/2005/ drugsafety0301.html.

The FDA's own Science Board has expressed similar alarm about the agency's ability to protect the public from pharmaceutical products. In December 2006, the FDA Commissioner asked its Science Board to form a Subcommittee to assess whether science and technology at the FDA could support current and future regulatory needs. The Science and Technology Subcommittee consisted of members of the Science Board and experts representing industry, academia, and other government agencies.

In a 2006 report titled "FDA Science and Mission at Risk," the Subcommittee found that demands placed on the FDA have increased dramatically due to the advance of scientific discoveries, the complexity of new products submitted for the FDA's review, the emergence of challenging safety problems, and the globalization of the industries that the FDA regulates. *See* FDA Science Board Report at 3. At the same time, the Subcommittee concluded, "the scientific demands on the Agency far exceed its capacity to respond. This imbalance is imposing a significant risk to the integrity of the food, drug, cosmetic and device regulatory system, and hence the safety of the public." *Id.* at 2. In particular, the Subcommittee found that the FDA's scientific base has eroded and its scientific organization structure is unacceptably weak. "Today, not only can the Agency not lead, it cannot even keep up with the advances in science." *Id.* at 3. Moreover, because the FDA's scientific workforce lacks expertise in numerous fields, "the FDA is ineffective in responding to emerging fields that require individuals and work teams with multidisciplinary skills built on very complex, highly

specialized, often esoteric bodies of knowledge." *Id.* at 5. The Subcommittee also found that the FDA's information technology infrastructure is so antiquated and unstable that "[t]he IT situation at FDA is problematic at best – and at worst it is dangerous." *Id.* at 5. The Subcommittee bluntly addressed the FDA's funding problems: "In contrast to previous reviews that warned crises would arise if funding issues were not addressed, recent events and our findings indicate that some of those crises are now realities and American lives are at risk." *Id.* at 6 (emphasis added).

The Subcommittee discussed the above problems specifically in the context of post-marketing drug safety. The Subcommittee specifically found that "[t]he FDA lacks sufficient expertise to understand the impact of [drug] product use, to maintain ongoing currency with their evolution or to evaluate the sophisticated products produced. In addition, the FDA has no consistent strategy to acquire that expertise." *Id.* at 24. These deficiencies, the Subcommittee said, are compounded by the agency's inadequate information technology infrastructure, which cannot effectively manage the large amounts of data created by emerging sciences (such as genomics, proteomics, and metabolomics) in support of product design, testing, and ongoing safety analysis. *See id.* at 25-26.

These grim conclusions have been echoed by Subcommittee member Peter Barton Hutt, a former Chief Counsel of the FDA. During recent congressional testimony, Mr. Hutt stated that "[s]cience at the Food and Drug Administration (FDA) today is in a precarious position. In terms of both

personnel and the money to support them, the agency is barely hanging on by its fingertips." *See* Testimony of Peter Barton Hutt before the U.S. House Subcommittee on Oversight and Investigations of the Committee on Energy and Commerce (Jan. 29, 2008) at 1, available at http://energycommerce.house.gov/cmte_mtgs/110-oi-hrg.012908.Hutt-Testimony.pdf (emphasis added). Mr. Hutt added that "FDA has become a paradigmatic example of the 'hollow government' syndrome – an agency with expanded responsibilities, stagnant resources, and the consequent inability to implement or enforce its statutory mandates." *Id.* at 2.

None of this has been lost on Congress. In January 2008, three Senators and five Representatives, all committee chairs, wrote the FDA Commissioner about an FDA effort to limit the circumstances under which companies must update drug labels with new safety information. Criticizing the effort, the authors emphasized the FDA's dire funding situation:

> Since 1982, FDA's funding situation has taken a dramatic turn for the worse. Today, FDA is an agency that is all but starved of resources. Experts from every affected sector agree that this desperate funding situation has rendered FDA unable to protect the American public from even the most basic threats, including contaminated food, tainted and dangerous drugs, and faulty medical devices. According to FDA's own Science

> Board, FDA's ability to carry out its mission is so compromised by loss of resources that American lives are now at risk.

See Correspondence from Senators Leahy, Kennedy and Dodd and from Representatives Waxman, Dingell, Markey, Pallone, and DeLauro, dated Jan. 23, 2008, available at http://oversight.house.gov/documents/20080123120931.pdf.

In short, the Petitioner advances a preemption argument with the implicit premise that Americans can rely on the FDA to ensure that drugs are appropriately labeled. This premise is faulty in large part because the FDA is so inadequately funded and understaffed with respect to protecting drug safety. That risk will only increase if the FDA is forced to be the sole guarantor of drug safety.

II. The FDA lacks the independence to ensure drug safety.

Because of its limited resources, the FDA must rely on the industry it regulates to perform essential functions of the FDA's mission. For example, the agency relies entirely on the pharmaceutical industry to perform clinical research on drugs being reviewed; the agency does not conduct independent research on a drug's capabilities or adverse effects. *See* IOM Report at 2-4. This reality is not without consequences. As two former editors-in-chief of the New England Journal of Medicine have observed, "[c]ompanies now often insist on controlling how the

research is done and reported, and whether the result will even be published at all" under "financial arrangements with academic medical centers and their faculties . . . that threaten the objectivity and credibility of clinical research." Marcia Angell & Arnold S. Relman, Op-Ed, *Prescription for Profit*, Wash. Post, June 20, 2001, at A27. In other words, the FDA sees only what a drug company provides with regard to clinical testing of a pharmaceutical product, and that information may not even be reliable.

Not only does the FDA receive only those materials that the drug companies provide, but the FDA relies heavily on drug companies to finance the agency's review of that material. In 2004, for example, more than half of the FDA's budget for review of drug applications for human drugs was obtained from industry-provided user fees. *See* FY 2004 PDUFA Financial Report Required by the PDUFA, at 9 (March 2005), available at www.fda.gov/oc/pdufa/finreport2004.

Further, many of FDA's scientific personnel have said that commercial interests routinely affect the FDA's decision-making process. Sixty percent of FDA scientists responding to the 2006 UCS Poll knew of cases where commercial interests inappropriately influenced FDA approvals or other decisions. *See* Union of Concerned Scientists, *Voices of Scientists at FDA: Protecting Public Health Depends on Independent Science* at 2 (2006), available at http://www.ucsusa.org/scientific_integrity/interference/fda-scientists-survey-summary.html. One-fifth of the survey respondents also reported being "asked

explicitly by FDA decision-makers to provide incomplete, inaccurate or misleading information to the public, regulated industry, media, or elected/senior government officials." *Id.* Overall, FDA's scientists reported "significant interference with the FDA's scientific work." *See id.* at 1.

The FDA relies not only on industry money, but also frequently on industry scientists to advise the FDA on a drug's risks and benefits. Unfortunately, these scientists are often subject to unacceptable conflicts of interest. A recent study published in the Journal of the American Medical Association found that almost one-third of the scientists on product review panels had financial interests exceeding $50,000 in the company whose products they were responsible for evaluating. *See* Peter Lurie et al., *Financial Conflict of Interest Disclosure and Voting Patterns at Food and Drug Administration Drug Advisory Committee Meetings*, 295 J. Am. Med. Ass'n 1921, 1924 (2006). The study also found that more than one-fifth of product review panels included a majority of scientists with a conflict of interest, and that nearly three-quarters of such panels included at least one scientist with a conflict of interest. *See id.*

The FDA's lack of independence from the pharmaceutical industry necessarily weakens the FDA's ability to monitor and promote drug safety. The danger to the public created by this lack of independence will increase if the FDA becomes the sole guarantor of drug safety.

III. The FDA lacks the regulatory tools to ensure drug safety.

Finally, resource constraints aside, the FDA lacks effective regulatory authority to require a manufacturer to enhance a drug's warnings after the drug has gone on the market. This further limits the FDA's ability to ensure that drugs are safe and appropriately labeled.

By way of background, since the passage of the Food, Drug and Cosmetic Act in 1938, all drugs must be evaluated and approved by the FDA before they may be marketed in the United States. Since 1962, a drug's sponsor must obtain FDA approval that a new drug is safe and effective for its approved uses and that its labeling is not false or misleading. *See* 21 U.S.C. § 355. The FDA's review of a new drug includes examination of the drug's label, which must accurately and fairly describe the drug's intended uses and must discuss its potential risks, contraindications, warnings, precautions and adverse reactions. *See* 21 U.S.C. § 355(d); 21 C.F.R. §§ 201.56, 201.57, 201.80.

To obtain FDA approval for a new drug, the drug's sponsor must perform clinical studies bearing on the drug's safety and effectiveness, and provide the results of those studies in a "New Drug Application." *See* 21 U.S.C. § 355. Unfortunately, pre-approval clinical studies typically involve carefully controlled study conditions and at most a few thousand subjects who may not represent the full array of patients who will use the drug when it is placed on the market. *See* IOM Report at 2-6, 2-7. As a result, clinical studies

often are incapable of detecting unforeseen and serious side-effects that will not become apparent until the drug is widely prescribed by doctors, even where the drug is properly used for its approved purposes. *See id.*; Kessler and Vladeck, 96 Geo. L.J. at 470.

Because of the likelihood that unforeseen adverse effects will manifest after a drug is on the market, FDA regulations enable a drug's sponsor to enhance the drug's label without FDA's pre-approval. *See* 21 C.F.R. §§ 201.57(c)(6), 201.80(e), 314.70(c). Unfortunately, the FDA historically has had no authority to impose a post-approval labeling change on a manufacturer unwilling to meet its responsibilities. Instead, the FDA has been forced to negotiate with manufacturers on labeling issues, using as leverage its powers to seek withdrawal of dangerous drugs from the market or to file a misbranding action. *See* 21 U.S.C. §§ 331, 355(e). Unfortunately, these powers are too drastic to be used with any frequency, crippling the FDA's leverage to force a desired change. For example, since 2000, there have been only 10 drug withdrawals for safety reasons, and in each case the drug's sponsor voluntarily removed the drug from the market. *See* GAO Report at 10 (noting that the FDA has forcibly withdrawn a drug only once in its history). As for misbranding claims, the FDA has <u>never</u> filed a misbranding claim against a manufacturer on grounds that a drug's warnings were inadequate. *See* Vladeck and Kessler, 96 Geo. L.J. at 479-80 (noting that misbranding actions are resource intensive and difficult to prove). Because drug manufacturers know there is little credibility to an FDA threat that it will forcibly remove drugs from the market or commence a

misbranding action on labeling issues, the FDA lacked a strong negotiating position, resulting in compromise agreements that provide the public with less protection than the FDA initially sought. *See id.* at 480 and note 82.

This situation is not dramatically improved by recent Congressional action to strengthen the FDA's authority. Recognizing that regulatory deficiencies have contributed to the FDA's overall ineffectiveness, Congress recently enacted the FDAAA, *inter alia*, to provide the FDA with some authority to prompt manufacturers to make labeling changes. *See* 21 U.S.C. § 355(o). Unfortunately, the statute limits that power by requiring the FDA to undertake negotiations with a drug manufacturer before taking action, and by failing to provide the FDA with the power to act unilaterally or immediately. The FDAAA alone is not a warrant to jettison the tort system.

By way of further explanation, the FDAAA requires the FDA to notify a drug's manufacturer if the agency becomes aware of new safety information the agency believes should be included in a drug's labeling. *See* 21 U.S.C. § 355(o)(4)(A). Following the notification, the manufacturer has thirty days either to propose label changes reflecting the new safety information or to notify the FDA that it does not believe labeling changes are warranted. *See* 21 U.S.C. § 355(o)(4)(B). If the FDA disagrees with the manufacturer's response, the FDA must initiate "discussions" to reach agreement with the manufacturer. *See* 21 U.S.C. § 355(o)(4)(C). These discussions supposedly may not extend more than

thirty days, but the FDA has the authority to grant an extension. *See* 21 U.S.C. § 355(o)(4)(D). If the discussions result in agreement, that is the end of the matter; if they do not, then the FDA has fifteen days to order the manufacturer to make the changes the FDA deems appropriate. *See* 21 U.S.C. § 355(o)(4)(E). The manufacturer has five days within which to accede or file an appeal using dispute resolution procedures established by the FDA. *See* 21 U.S.C. § 355(o)(4)(F). If at the end of the appeal process, the FDA still concludes that changes are required to the label, the manufacturer must submit a supplement within fifteen days. *See* 21 U.S.C. § 355(o)(4)(G). Significantly, the statute does not enable the FDA to act unilaterally or immediately, although it gives the FDA power to "accelerate" the timelines where "a labeling change is necessary to protect the public health." 21 U.S.C. § 355(o)(4)(H).

This elaborate procedure raises practical questions about the efficacy of the statute. Because the FDA lacks sufficient resources to monitor drug safety effectively, the agency may never know that a drug needs enhanced warnings, or it may not initiate the FDAAA process in a timely fashion, or it may initiate the process but accept a poor compromise because other tasks call for attention. The statute also does nothing to address the ongoing influence of commercial interests on the FDA's decision-making process. The new authority provided by the FDAAA is limited where the FDA lacks the resources and independence to act effectively across the full range of drug safety issues. In any event, as the FDAAA did not exist at the time of the events giving rise to this

case, its bearing on this Court's analysis should be limited at best.

* * *

The Petitioner invites this Court to leave drug safety solely to the care of the FDA, an agency so constrained by lack of funding, personnel, and scientific expertise that "American lives are now at risk." FDA Science Board Report at 6. This Court should reject that invitation, and preserve the historic partnership between the FDA and tort system with regard to promoting public safety.

CONCLUSION

The judgment of the Vermont Supreme Court should be affirmed.

August 14, 2008

Respectfully submitted,

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IN THE

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WYETH,

Petitioner,

v.

DIANA LEVINE,

Respondent.

On Writ of Certiorari to the Vermont Supreme Court

BRIEF FOR THE AMERICAN ASSOCIATION FOR JUSTICE AS AMICUS CURIAE SUPPORTING RESPONDENT

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08-1249-C

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INTEREST OF AMICUS CURIAE

The American Association for Justice ("AAJ"), formerly the Association of Trial Lawyers of America, respectfully submits this brief as *amicus curiae* in support of Respondent. This brief is filed with consent of all parties.[1]

AAJ is a voluntary national bar association whose trial lawyer members primarily represent individual plaintiffs in personal injury cases and other civil actions, including product liability cases. Throughout its history, AAJ has advocated in courts, in Congress, and in state legislatures to preserve the protections for ordinary citizens afforded by the common law and to ensure that state tort claims, such as product liability claims, provide injured persons with effective legal recourse and remedies for wrongful injuries. By bringing such claims on behalf of people injured by drug products and by testifying before Congress about drug safety and the FDCA, AAJ's members have helped to ensure that the nation's consumers have access to safe and effective pharmaceuticals.

SUMMARY OF ARGUMENT

A common law cause of action against drug manufacturers for failure to provide adequate warnings has been recognized for over 150 years and has coexisted with federal regulation for a century.

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[1] Letters of consent from both parties have been filed with the Clerk of Court. Pursuant to Rule 37.6, *amicus* states that no counsel for a party authored any part of this brief, nor did any person or entity other than *amicus*, its members, or its counsel make a monetary contribution to its preparation or submission.

Congress, through multiple revisions of the Food, Drug, and Cosmetic Act, has consistently declined to preempt such state tort litigation. For good reasons Congress and, until recently, the FDA viewed state tort liability as an important complement to federal regulation in ensuring safe and effective drugs.

State tort law has always taken a drug company's compliance with FDA requirements into account as evidence that the company was not negligent. Once a defendant demonstrates such compliance, the plaintiff must come forward with evidence that a reasonable company would have done more under the circumstances, as Diana Levine did in this case. This focus on the special circumstances of the case ensures that a finding of liability will not pose a "direct and positive conflict" with FDA regulatory decisions.

Virtually every state and Congress has declined to elevate compliance with FDA requirements into a dispositive defense. They recognize that such a defense would be difficult to apply, place excessive reliance on the FDA, undermine incentives for drug companies to strengthen their warnings, and leave injured persons remediless. This Court must not now create a national FDA compliance affirmative defense under the guise of implied conflict preemption.

ARGUMENT

I. Federal Regulation of Prescription Drugs and State Tort Liability for Inadequate Warnings Have Coexisted Compatibly For a Century.

A. A Common Law Cause of Action for Failure to Warn of the Risks Posed by Drugs is Long-Standing and Widely Recognized.

A common law cause of action for negligence with respect to the manufacture, sale, and administration of medicines and related products predates federal regulation of pharmaceuticals and is widely recognized and accepted. *See Thomas v. Winchester*, 6 N.Y. 397, 1852 WL 4748 (N.Y. 1852) (holding a drug manufacturer who carelessly labeled a poison as a harmless medicine and sold the mislabeled medicine liable for a patient's resultant injury). Where, as here, there has been a "long history of tort litigation" in the area of state common law at issue, the presumption against preemption has "add[ed] force." *Bates v. Dow Agrosciences LLC*, 544 U.S. 431, 449 (2005).

State courts have held drug manufacturers liable for injuries resulting from failures to adequately warn of the risks and potential side-effects associated with their products since at least the mid-nineteenth century. *See, e.g. Norton v. Sewall*, 106 Mass. 143, 1870 WL 3529 (Mass. Nov. 1870); *Blood Balm Co. v. Cooper*, 83 Ga. 457, 10 S.E. 118 (Ga. 1889); *Peters v. Johnson*, 50 W. Va. 644, 41 S.E. 190 (W. Va. 1902). In *Thomas v. Winchester*, for example, the court held that, although the drug

manufacturer's "sale of the poisonous article was made to a dealer in drugs, and not to a consumer," the manufacturer had a duty to the ultimate consumer to warn of possible risks attendant to the drug and to adequately label the drug:

> The defendant's duty [to the consumer] arose out of the nature of his business and the danger to others incident to its mismanagement. Nothing but mischief like that which actually happened could have been expected from sending the poison falsely labeled into the market; and the defendant is justly responsible for the probable consequences of the act.

1852 WL 4748, at *9.

Congress first regulated food and drugs in the Federal Food and Drugs Act of 1906, 21 U.S.C. §§ 1, *et seq*. The 1906 act was intended to "prevent the misuse of the facilities of interstate commerce in conveying to and placing before the consumer misbranded and adulterated articles of medicine or food . . . ." *McDermott v. Wisconsin*, 228 U.S. 115, 131 (1913). Congress did not address state tort liability in the 1906 act, implicitly indicating that it did not intend to restrict such well-established causes of action, which furthered the purposes of the act by providing remedies for persons who wrongly suffered drug-related injuries. As this Court explained only a few years after the statute was enacted, "it by no means follows that the state is not permitted to make regulations, with a view to the protection of its people against fraud or imposition by impure food or drugs." *Id.*

After the 1906 act was enacted, common law failure to warn litigation continued unconstrained. *See, e.g., Hruska v. Parke, Davis & Co.*, 6 F.2d 536 (8th Cir. 1925) (holding that a manufacturer's negligence in preparing or selling a pharmaceutical product is actionable by a consumer or third party who suffers from the negligence); *Marigny v. Dejoie*, 172 So. 808 (La. Ct. App. 1937) (holding pharmacist liable for plaintiff's injuries resulting from ingestion of mislabeled drug); *Boyd v. Coca Cola Bottling Works*, 177 S.W. 80, 81 (Tenn. 1915) (holding that drug, food, and beverage manufacturers owe a duty to those who consume their products and that "[a] tort is committed, a legal right invaded, by practices which prejudice another's health"); *see also Mazetti v. Armour & Co.*, 135 P. 633 (Wash. 1913) (holding that restauranteur could bring action against food manufacturer when restaurant patron was injured by manufacturer's product, which was regulated by, and violated, the 1906 act). During this period, various states also enacted complementary laws to "provide the particular consumer and the general public with a higher and surer degree of protection than is afforded by exclusive recourse to common-law remedies." *McClanahan v. California Spray-Chem. Corp.*, 75 S.E.2d 712, 717-18 (Va. 1953) (discussing 1906 act and subsequently enacted state laws).

Congress revisited, and strengthened, federal regulation of food and drugs in 1938, when it enacted the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. §§ 301-392 ("FDCA"). Congress did not attempt to limit the state tort liability of pharmaceutical manufacturers in the FDCA, or in any of its subsequent amendments, as discussed below. *See infra* at 5-6.

Moreover, even after the enactment of the FDCA, persons injured by prescription drugs continued to sue drug companies for inadequate warnings. *See Riegel v. Medtronic*, ___ U.S. ___, 128 S.Ct. 999, 1017 (2008) (Ginsburg, J., dissenting) (from passage of FDCA through 1976 Medical Device Amendments, "state common-law claims for drug labeling and design defects had continued unabated"); *see, e.g., Marcus v. Specific Pharms., Inc.*, 82 N.Y.S.2d 194, 194 (N.Y. Sup. Ct. 1948) (denying drug company's motion to dismiss failure-to-warn claims, because "[o]ne who manufactures and distributes an article which, if improperly used, is dangerous to human life is under a duty to apprise the purchasing public by labels or otherwise of the manner in which the article may be safely used"); *Webb v. Sandoz Chem. Works, Inc.*, 69 S.E.2d 689, 692 (Ga. Ct. App. 1952) (holding that plaintiff stated a cause of action for failure-to-warn sufficient to withstand motion to dismiss, but that evidence proffered later showed that defendant had provided adequate warning); *Love v. Wolf*, 249 Cal. App. 2d 822, 832 (Cal. Ct. App. 1967) (finding drug manufacturer liable for plaintiff's injuries based on both inadequate warning on the drug's label and overpromotion); *Reyes v. Wyeth Labs.*, 498 F.2d 1264 (5th Cir. 1974) (affirming holding that manufacturer could be liable for failure to warn consumer of adverse events and unreasonably dangerous conditions related to drug). And this failure-to-warn cause of action was expressly preserved in the most recent restatement: "A manufacturer of a prescription drug . . . is subject to liability for harm to persons caused by . . . [a] prescription drug . . . [that] is not reasonably safe due to inadequate instructions or warnings." Restatement (Third) of Torts: Prods. Liab. § 6 (1998)

As evidence that no one perceived that state tort litigation conflicted with federal drug regulation, pharmaceutical defendants in these suits generally did not even raise the defense of federal preemption. *See Riegel*, 128 S.Ct. at 1017 n.11 (Ginsburg, J., dissenting) ("Most defendants, it appears, raised no preemption defense to state tort suits involving FDA-approved drugs.") (collecting cases); *see also* cases cited *supra* 7 (in none of the afore-referenced cases did defendants raise a preemption defense).

Only since the late 1980s have drug company defendants regularly argued for preemption. *See, e.g., In re Tetracycline Cases*, 747 F. Supp. 543 (W.D. Mo. 1989) (rejecting defendant drug manufacturer's argument that the federal regulation of drug labels and package inserts preempted plaintiffs' claims). And, with few exceptions, courts have consistently rejected the defense of preemption in cases in which it was raised. *See Riegel*, 128 S.Ct. at 1018-19 & n.16 (Ginsburg, J., dissenting) ("Courts that have considered the question have overwhelmingly held that FDA approval of a new drug application does not preempt state tort suits.") (collecting cases); *Abbot by Abbot v. Am. Cyanamid Co.*, 844 F.2d 1108, 1112 n.1 (4th Cir. 1988) ("The overwhelming majority of courts considering federal preemption of state law as regards vaccines have found no preemption.") (collecting cases); *see, e.g., id.* at 1111 (holding that in the FDCA "Congress did not intend, either expressly or impliedly, to preempt state law"); *Caraker v. Sandoz Pharms. Corp.*, 172 F. Supp. 2d 1018 (S.D. Ill. 2001); *Tobin v. Astra Pharm. Prods., Inc.*, 993 F.2d 528 (6th Cir. 1993); *Osburn v. Anchor Labs., Inc.*, 825 F.2d 908, 913 (5th Cir. 1987); *Feldman v. Lederle Labs.*, 479 A.2d 374 (N.J. 1984); *Kociemba v. G.D. Searle & Co.*, 680 F. Supp. 1293,

1299 (D. Minn. 1988) ("The mere fact that the Cu-7 received FDA approval does not, by itself, indicate that Congress impliedly intended to preclude state tort actions against prescription drug manufacturers."). Even after the FDA, in the current administration, began to assert that state tort liability and federal regulation conflict, most courts continue to reject the preemption defense. *See, e.g., In re Vioxx Prods. Liab. Litig.*, 501 F. Supp. 2d 776, 785 (E.D. La. 2007); *In re Zyprexa Prods. Liab. Litig.*, 489 F. Supp. 2d. 230, 273-74 (E.D.N.Y. 2007); *Perry v. Novartis Pharm. Corp.*, 456 F. Supp. 2d 678 (E.D. Pa. 2006).

B. Congress and, Until Recently, the FDA Regarded State Tort Liability and Federal Regulation As Complementary.

1. Congress Has Shown No Intention To Preempt Common Law Tort Claims Concerning Prescription Drugs.

Congress enacted the FDCA in 1938 to remedy defects in the 1906 Act. Among other things, the earlier law had "fail[ed] to take cognizance of fraudulent statements covering food or drugs which are not in or upon the food or drug package." Secretary of Agriculture, *Annual Report for the Fiscal Year ended June 30, 1933*, 1, 13-14 (citing The Chief of the Bureau of Chemistry, *Annual Report 1917*), *quoted in Federal Food, Drug, and Cosmetic Act: A Statement of its Legislative Record* 24-25 (Charles Wesley Dunn, ed. 1938).

The revised Food and Drugs Act was first introduced in the Senate in 1933 as S. 1944. S. 1944

contained a provision titled Liability for Personal Injury, which stated: "A right of action for damages shall accrue to any person for injury or death proximately caused by a violation of this Act." *Id.* at 49 (citing S. 1944, as introduced in the 73d Congress, 1st Session, June 6, 1933). This provision, however, was not included in future versions of the act. Apparently, Congress decided not to create a federal cause of action for damages because, as witnesses testified, it was unnecessary: "[a] common law right of action [already] exists." *Hearings on S. 1944 Before a Subcomm. of the S. Comm. on Commerce*, 73d Cong., 2d Sess. 400 (1933) (statement of W.A. Hines); *id.* at 403 (statement of J.A. Ladds) ("This act should not attempt to modify or restate the common law with respect to personal injuries."); *see also Riegel*, 128 S.Ct. at 1017 n.10 (Ginsburg, J., dissenting) (quoting same). A key way to accomplish the FDCA's purpose of protecting the public was by retaining common law tort liability for personal injuries.

By passing the FDCA without a private right of action, Congress affirmed its intent that state tort actions would remain available to provide "judicial recourse for those injured." As this Court has observed in similar contexts:

> [Congress'] silence [regarding state law remedies for persons injured by radiation from a nuclear plant] takes on added significance in light of Congress' failure to provide any federal remedy for persons injured by such conduct. It is difficult to believe that Congress would, without comment, remove all

> means of judicial recourse for those injured by illegal conduct.

Silkwood v. Kerr-McGee Corp., 464 U.S. 238, 251 (1984); *see also Medtronic, Inc. v. Lohr*, 518 U.S. 470, 487 (1996) (citing same in construing 21 U.S.C. § 360k(a) of the Medical Device Amendments).

Congress revisited federal food and drug regulation in the 1962 Drug Amendments, which "shifted the burden of proof from FDA (which previously had to prove harm to keep a drug from being marketed) to manufacturers, who now were required to demonstrate both safety and efficacy prior to receipt of marketing approval." Institute of Medicine, Committee on the Assessment of the U.S. Drug Safety System, *The Future of Drug Safety: Promoting and Protecting the Health of the Public*, 152 (Alina Baciu, *et al.* eds. 2007) ("IOM Report") (citation omitted).

The 1962 amendments clarified the FDCA's intended relationship to state law. Congress included language explicitly *restricting* the potential preemptive effect of federal law to cases of "direct and positive conflict":

> Nothing in the amendments made by this Act to the Federal Food, Drug, and Cosmetic Act shall be construed as invalidating *any* provision of State law which would be valid in the absence of such amendments unless there is a *direct and positive conflict* between such amendments and such provision of State law.

Pub. L. No. 87-781, § 202, 76 Stat. 780, 793 (1962) (emphasis added). When Congress's express words provide "a 'reliable indicium of congressional intent with respect to state authority, there is no need to infer congressional intent to pre-empt state laws.'" *Cipollone v. Liggett Group, Inc.*, 505 U.S. 504, 517 (1992) (citation omitted).

Congress inserted the "direct and positive conflict" language in the 1962 Drug Amendments to limit claims of preemption. *See Thrall v. Wolfe*, 503 F.2d 313, 317 (7th Cir. 1974) (interpreting statute with *identical* "direct and positive conflict" language and concluding: "The section was doubtless inserted for the purpose of avoiding a claim of preemption"). "[D]ebates on the adoption of this provision expressly noted that the provision was consistent with the intention that federal law should not preempt in those fields where state food and drug laws are stronger." *Merrell Dow Pharms., Inc. v. Oxendine*, 649 A.2d 825, 828 n.3 (D.C. 1994) (citing 108 Cong. Rec. 21,083 (1962)). As the court below correctly concluded, the "plain language of the [FDCA] indicates that Congress did not intend to interfere with state prerogatives except where doing so is absolutely necessary, . . . and the plain language of the regulation [at issue] makes such interference unnecessary here." *See Levine v. Wyeth*, 944 A.2d 179, 191 (Vt. 2006).

Congress knows how to write an express preemption provision when it wants to: in subsequent amendments to the FDCA, Congress enacted express statutory preemption provisions applicable to medical devices, over-the-counter (OTC) drugs, and cosmetics. 21 U.S.C. § 360k(a) (1976); 21

U.S.C. § 379r (1997); 21 U.S.C. § 379s (1997).[2] But Congress never adopted any comparable preemptive language concerning prescription drugs, thereby further evidencing its intent not to preempt state law.

Most recently, in 2007, Congress enacted the Food and Drug Administration Amendments Act of 2007, Pub. L. No. 110-85, 121 Stat. 823. That act bolsters the FDA's authority to require a manufacturer to change a drug label if the agency becomes aware of information it believes should be included. 121 Stat. at 924 (to be codified at 21 U.S.C. §355 (o)(4)). To defuse claims that this expanded agency authority would lead to preemption, Congress included a "rule of construction" to make clear that the act did not "affect the responsibility of" a drug company "to maintain its label in accordance with existing requirements," including 21 C.F.R. §§ 201.80 (e) and 314.70(c). 121 Stat. at 925-26 (to be codified at 21 U.S.C. § 355(o)(4)(I)). These are the regulatory provisions invoked by many courts, including the court below, as grounds for rejecting drug company assertions of implied conflict preemption. Thus, here again, Congress indicated its intention not to preempt state tort law. *See* 153 Cong. Rec. S11833 (daily ed. Sept. 20, 2007) (statement of Sen. Kennedy) ("Congress has stated very clearly in the legislation that we do not intend the new authority being given to the FDA to preempt common law liability for a drug company's failure to warn its customers of health risks").

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[2] The preemption provisions applicable to OTC drugs and cosmetics include savings clauses that expressly exempt state product liability claims from preemption. 21 U.S.C. § 379r(e); 21 U.S.C. § 379s(d).

Congress has had numerous opportunities over the past seventy years to limit common law remedies for drug-related injuries, but has repeatedly declined to do so. Congress, instead, has emphasized that state law should not be preempted, except in cases where a "direct and positive conflict" exists.

2. The FDA, Prior to this Decade, Regarded State Tort Liability and Federal Regulation As Complementary.

The FDA itself also has recognized the utility of state products liability claims, and historically has not contended that such claims are preempted. In 1994, for example, when the FDA acted to prevent disclosure of the identities of patients and other persons involved with adverse event reports, the agency took pains to make clear that the action was "not intended to frustrate or impede tort litigation in this area. Indeed, FDA recognizes that product liability plays an important role in consumer protection." 59 Fed. Reg. 3944, 3948 (Jan. 27, 1994). That same year, the Chief Counsel of the FDA, Margaret Jane Porter, wrote to explain the agency's anti-preemption position in *Medtronic, Inc. v. Lohr*: "FDA product approval and state tort liability usually operate independently, each providing a significant, yet distinct, layer of consumer protection." Margaret J. Porter, *The Lohr Decision: FDA Perspective and Position,* 52 Food & Drug. L.J. 7, 11 (1997).

On at least two occasions, the FDA has explicitly stated that its labeling regulations do not have preemptive effect. In a 2000 Notice of Proposed Rulemaking to revise those requirements, the agency

asserted that the proposed amendments "do[] not contain policies that have federalism implications or that *preempt* State law." 65 Fed. Reg. 81,082, 81,103 (Dec. 22, 2000) (emphasis added). Similarly, at oral argument in *Buckman Co. v. Plaintiff's Legal Committee,* Oral Arg. Official Trans., No.98-1768, 2000 WL 1801621 (Dec. 4, 2000), the Solicitor General's office, on behalf of the FDA, distinguished the fraud-on-the-FDA claim at issue in that case from traditional common law tort claims: "The fraud claim is preempted, but if there is negligent design, negligent manufacturing, failure to warn, common law malpractice, all of those claims are available" and are not preempted. *Buckman* Oral Arg. Official Trans., 2000 WL 1801621, at *21.

On yet other occasions, the FDA has expressed its view that state tort litigation does not conflict with or pose an obstacle to the agency's mission. In 1979, when the agency issued its final rule regarding prescription drug labeling, the rulemaking notice affirmed: "It is not the intent of the FDA to influence the civil tort liability of the manufacturer . . . ." 44 Fed. Reg. 37,434, 37,437 (Jun. 26, 1979). More explicitly, the rulemaking notice accompanying a 1998 final regulation on Patient Medication Guides stated that:

> FDA does not believe that the evolution of state tort law will cause the development of standards that would be at odds with the agency's regulations. FDA's regulations establish the minimal standards necessary, but were not intended to preclude the states from imposing additional labeling requirements. States may authorize

> additional labeling but they cannot reduce, alter, or eliminate FDA-required labeling.

63 Fed. Reg. 66,378, 66,384 (Dec. 1, 1998).

The FDA recognized that its regulatory efforts benefited from and were supplemented by state product liability litigation, such as that brought by Respondent here. As former FDA Commissioner David Kessler has written, it was

> the FDA's view that its regulatory efforts could comfortably coexist with state-law damages claims by consumers injured by drugs. As the agency saw it, state-law failure-to-warn litigation *did not* interfere with the agency's regulatory efforts. . . . State damages litigation helps uncover and assess risks that are not apparent to the agency during a drug's approval process. Until recently, in the FDA's view, this "feedback loop" enabled the agency to better do its job. The agency also wanted to avoid the "harsh implications" of eliminating "judicial recourse for consumers injured by defective" drugs.

David A. Kessler, M.D. & David C. Vladeck, *A Critical Examination of the FDA's Efforts to Preempt Failure-to-Warn Claims*, 96 Geo. L.J. 461, 463 (2008) (emphasis added) (quoting Margaret J. Porter, *The Lohr Decision: FDA Perspective and Position*, 52 Food & Drug L.J. at 9).

Of course, in the past several years, the FDA's position has undergone a "seismic shift"; "[t]he agency now maintains that state law failure-to-warn cases threaten its ability to protect the public health." *Id.* But this Court should not ignore the agency's historic understanding that state tort litigation complemented the federal regulatory scheme.

C. State Tort Liability Supports Federal Regulation in Advancing Congress's Goal of Safe and Effective Pharmaceuticals.

Litigation is crucial to ensure the safety and effectiveness of drugs because, as Congress recognized, and the Institute of Medicine recently confirmed, FDA approval is not a guarantee of safety or efficacy and the FDA historically has lacked the tools to fully and adequately regulate drugs after they are on the market. *See* IOM Report, *supra*, 151-76. The FDA's reach is enormous, regulating "approximately $1 trillion in consumer products or 25 cents of every consumer dollar expended in this country annually." FDA Subcommittee on Science & Technology, *FDA Science & Mission at Risk* 1 (Nov. 2007) ("*Mission at Risk*"). Yet, as the FDA itself has concluded, the agency has "serious scientific deficiencies and is not positioned to meet current or emerging regulatory responsibilities." *Id.* at 2-3. The FDA is underfunded and overburdened, and needs "substantially increased resources in both funds and personnel" if it is to carry out the tasks assigned to it. IOM Report, *supra*, 197-98.

State common law provides an important supplement to this overtaxed regulatory system. *See*

In re Zyprexa Prods. Liab. Litig., 493 F. Supp. 2d. 571, 575 (E.D.N.Y. 2007) ("[L]awyers and their clients often find themselves serving as drug safety researchers of last resort.") (quotation omitted). Private tort litigation has "helped the medical community reassess drugs by bringing to light new information about adverse effects" and, "[i]n both the premarketing and postmarketing stages, lawsuits have helped uncover important and previously unavailable data about major adverse events." Aaron S. Kesselheim & Jerry Avorn, *The Role of Litigation in Defining Drug Risks*, 297 JAMA 308 (Jan. 17, 2007).

Product liability claims, such as those brought by Respondent, work in concert with federal regulation, allowing the marketplace to provide an added financial incentive for manufacturers to make their products safe and effective as mandated by the FDCA. *See* John W. Wade, *On the Nature of Strict Tort Liability for Products*, 44 Miss. L.J. 825, 826 (1973); *see also* W. Kip Viscusi, *Reforming Products Liability* 66 (1991) ("The purpose of products liability is to fill the gaps left by market imperfections and to replicate the incentives that would have been generated had markets been functioning perfectly."). Moreover, by assessing risk retrospectively, product liability helps to compensate consumers for imperfect information. Steven P. Croley & Jon D. Hanson, *Rescuing the Revolution: The Revived Case for Enterprise Liability*, 91 Mich. L. Rev. 683, 707-08 (1993); State tort claims fulfill these roles directly, by providing remedies to people who suffer injuries from drugs, and also indirectly, by creating financial incentives for drug companies to update the warnings on their products' labels to reflect current knowledge about the dangers those products pose.

In addition, "tort law often informs regulatory decisions, and the FDA has often acted in response to information that has come to light in state damages litigation." Kessler & Vladeck, 96 Geo. L.J. at 477 (citing *Bates*, 544 U.S. at 451; *see also* Karen E. Lasser, *et al.*, *Timing of New Black Box Warnings & Withdrawals for Prescription Medications*, 287 JAMA 2215, 2218 (2002). The "legal system [has] played an important role in spurring change in regulatory or corporate procedures, as well as extending knowledge about drug risks by adding to the evidence available for evaluation by physicians, patients, and regulators." Kesselheim & Avorn, *supra*, at 310.

In all of these ways state tort claims complement federal regulation and further the purposes of the FDCA. *Cf. CSX Transp., Inc. v. Easterwood*, 507 U.S. 658, 668 (1993) ("In fact, the scheme of [state] negligence liability could just as easily complement [federal] regulations"); *Silkwood*, 464 U.S. at 264 (Blackmun, J. dissenting) (stating that tort damages "complement the federal regulatory standards, and are an implicit part of the federal regulatory scheme"). As this Court said in *Bates v. Dow Agrosciences LLC* about a similar statutory scheme: "Private remedies . . . would seem to aid, rather than hinder, the functioning of FIFRA . . . . FIFRA contemplates that pesticide labels will evolve over time, as manufacturers gain more information about their products' performance in diverse settings. . . . [T]ort suits can serve as a catalyst in this process." 544 U.S. at 451.

Petitioner's and the FDA's arguments that Respondent's claims are preempted ignore the long coexistence of state tort law and federal regulation

and the structural complementarity between the two. This Court should reject these arguments and, instead, reaffirm that state tort claims advance the FDCA's goal of consumer protection and the regulatory objective of prompt and effective warnings of serious health risks.

II. State Tort Law Has Always Taken Compliance with Federal Regulatory Standards Into Account In Determining Liability.

How is it possible that, for nearly a century, neither courts nor legislators nor federal regulators perceived any significant conflict between state tort liability for failure to warn and federal regulation of prescription drugs? One principal reason is that state tort law has always taken federal standards into account, permitting pharmaceutical companies to introduce their compliance with federal labeling requirements as evidence of non-negligence. But, at the same time, every state recognized that this evidence could be overcome by other evidence of negligence or willful wrongdoing. Such an approach ensures that there will be no "direct and positive conflict" between state tort liability standards and federal regulation.

A. Under the Traditional Common Law Rule, Compliance with Federal Regulations is Evidence of Non-Negligence, But Not Dispositive.

The traditional rule has been set forth clearly in both the second and third restatements of tort law. Section 288C of the Second Restatement provides: "Compliance with a legislative enactment or an

administrative regulation does not prevent a finding of negligence where a reasonable man would take additional precautions." Restatement (Second) of Torts § 288C (1965). The Third Restatement reiterates this principle in the context of products liability claims, while clarifying that regulatory compliance is relevant and admissible evidence to be considered:

> In connection with liability for defective design or inadequate instructions or warnings: . . . (b) a product's compliance with an applicable product safety statute or administrative regulation is properly considered in determining whether the product is defective with respect to the risks sought to be reduced by the statute or regulation, but *such compliance does not preclude as a matter of law a finding of product defect.*

Restatement (Third) of Torts: Prods. Liab., § 4 (1998) (emphasis added).[3]

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[3] In a comment, the Restatement draws a sharp distinction between regulatory compliance and federal preemption. Section 4(b) of the Restatement:

> addresses the question of whether and to what extent, *as a matter of state tort law,* compliance with product safety statutes or administrative regulations affects liability for product defectiveness. . . .The safety statute or regulation may be a federal provision, but the decision to give it determinative effect is a state-law determination. In contrast, in federal preemption, the court decides *as a matter of federal law* that the relevant federal statute or

This treatment of regulatory compliance is a longstanding rule of common law. The principle was first prominently discussed by this Court in a case involving an accident at a railroad crossing, *Grand Trunk Railway Co. v. Ives*, 144 U.S. 408 (1892). As this Court observed:

> It is also held in many of the states (in fact the rule is well-nigh, if not quite, universal) that a railroad company, under certain circumstances, will not be held free from negligence, even though it may have complied literally with the terms of a statute prescribing certain signals to be given, and other precautions to be taken by it, for the safety of the traveling public at crossings.

Id. at 420-21; *see also Smith v. Maine Cent. R.R. Co.*, 32 A. 967, 970-71 (Me. 1895) ("[T]he statutes prescribing these special duties . . . do not constitute the sole measure of duty. The common law still requires the exercise of care and prudence commensurate with the degree of danger incurred. The statutes . . . do not release the company from the obligations to take such additional precautions as the peculiar circumstances of the case may demand."); *Catani v. Swift & Co.*, 95 A. 931, 933 (Pa. 1915) ("federal statutes providing for meat

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> regulation reflects, expressly or impliedly, the intent of Congress to displace state law, including state tort law, with the federal statute or regulation. . . . [T]he issue of defectiveness under state law is never reached.

Id., Comment e (emphasis added).

inspection by government officers do not relieve the packer from liability for damages [for breach of "common-law duty to sell only wholesome food"] where he has made no inspection nor taken any steps to ascertain for himself whether the meat sold by him is fit for food").

The rule has been applied repeatedly in failure-to-warn suits against pharmaceutical companies. *See, e.g., Stevens v. Parke, Davis & Co.*, 507 P.2d 653, 661 (Cal. 1973) ("mere compliance with regulations or directives as to warnings, such as those issued by the [FDA] here, may not be sufficient to immunize the manufacturer or supplier of the drug from liability....[W]hen the manufacturer or supplier knows of, or has reason to know of, greater dangers not included in the warning, its duty to warn may not be fulfilled."); *McEwen v. Ortho Pharm. Corp.*, 528 P.2d 522, 534 (Or. 1974) ("We hold that the warnings given by an ethical drug manufacturer may be found inadequate, '[a]lthough all of the government regulations and requirements have been satisfactorily met in the production and marketing of [the drug], and in the changes made in the literature'") (quoting *Yarrow v. Sterling Drug, Inc.*, 263 F. Supp. 159, 162 (D.S.D. 1967), *aff'd*, 408 F.2d 978 (8th Cir. 1969)); *Salmon v. Parke, Davis & Co.*, 520 F.2d 1359, 1362 (4th Cir. 1975) ("In North Carolina, as elsewhere, compliance with federal laws and regulations concerning a drug, though pertinent, does not in itself absolve a manufacturer of liability."); *Bristol-Myers Co. v. Gonzales*, 561 S.W.2d 801, 804 (Tex. 1978) ("fact that the package insert ... had been approved by the FDA did not relieve Bristol-Myers of its obligation to communicate an adequate warning to the users of this dangerous drug"); *MacDonald v. Ortho Pharm. Corp.*, 475

N.E.2d 65 (Mass. 1985) ("in instances where a trier of fact could reasonably conclude that a manufacturer's compliance with FDA labeling requirements or guidelines did not adequately apprise oral contraceptive users of inherent risks, the manufacturer should not be shielded from liability by such compliance."); *Wells v. Ortho Pharm. Corp.*, 788 F.2d 741, 746 (11th Cir. 1986) ("FDA determination that a warning is not necessary may be sufficient for federal regulatory purposes but still not be sufficient for state tort law purposes"); *O'Gilvie v. Int'l Playtex, Inc.*, 821 F.2d 1438, 1443 (10th Cir. 1987).

Indeed, an instruction based on this rule was given to the jury in this case:

> You may consider evidence of compliance by Wyeth with FDA requirements in obtaining approval for the Phenergan warning. Compliance with FDA requirements does not by itself establish that the warning was adequate for purposes of this case. You must decide whether the instructions and warnings were adequate based upon all the evidence presented in this trial including evidence about the FDA process.

See Jury Instructions, Printed Case, vol. II, at 348. Wyeth did not object to this instruction. *Id.*

Many courts have explained the rule on the grounds that most product safety statutes and regulations set only minimum safety standards. *See, e.g., Stevens*, 507 P.2d at 661 ("The warnings

required by such agencies may be only minimal in nature"). But it would perhaps be more precise to say that such regulations set a proper, legally sufficient standard only in the absence of any special circumstances. Restatement (Second) of Torts, § 288C, Comm. *a*. ("Where there are no such special circumstances, the minimum standard prescribed by the legislation or regulation may be accepted by the triers of fact, or by the court as a matter of law, as sufficient for the occasion; but *if for any reason a reasonable man would take additional precautions, the provision does not preclude a finding that the actor should do so.*") (emphasis added). Thus, once a defendant has demonstrated that its conduct conformed to all regulatory requirements, it becomes incumbent on the plaintiff to come forward with evidence to support the proposition that, under the circumstances, more should have been done.

Numerous pharmaceutical cases demonstrate the application of this rule. Where no special circumstances existed, courts have granted judgment as a matter of law to defendants that complied with FDA labeling requirements. *See, e.g., Chambers v. G.D. Searle & Co.*, 441 F. Supp. 377, 384 (D. Md. 1975) (where defendant had "no other information . . . indicating greater risks or dangers" than was available to FDA team that had developed package insert for oral contraceptive, it was reasonable for defendant to "rely on warnings approved by the entire group"); *Wolfgruber v. Upjohn Co.*, 423 N.Y.S.2d 95, 97-98 (App. Div. 1979) (summary judgment appropriate where "[t]he warning given was adequate by any standard and the plaintiff as a doctor knew the risks of taking this particular drug whose side effects were those specifically warned against as fully as defendant was able."); *Ramirez v.*

Plough, Inc., 863 P.2d 167, 175 (Cal. 1993) (Manufacturer of aspirin was not negligent as a matter of law for failing to include warnings in Spanish, where "FDA's regulations abundantly demonstrate its sensitivity to the issue of foreign-language labeling, and yet the FDA regulations do not require it").

In many other cases, where plaintiffs presented evidence that a reasonable drug company should have done more to warn of the dangers posed by its product, courts have concluded that the issue of negligence was for the jury. *Bristol-Myers Co. v. Gonzales* presents what may be the paradigmatic case: there officials at the defendant drug company knew "that the approved insert did not adequately warn of potential dangers . . . long before the inadequacy became known to the government." 561 S.W.2d at 804. But such plaintiffs' evidence has taken numerous other forms. In *Salmon*, for example, there was evidence that the defendant had resisted an FDA suggestion to strengthen the warning on an antibiotic, despite knowledge that physicians were ignoring the existing warning and using the drug carelessly to treat minor infections. 520 F.2d at 1363. In *Brochu v. Ortho Pharm. Corp.*, the court of appeals affirmed a jury verdict against a manufacturer of oral contraceptives that used the same label warnings on all of its products, even though it knew that the risk of stroke was far greater with its high-estrogen-dose pills. 642 F.2d 652, 657-59 (1st Cir. 1981). In *Hoffman v. Sterling Drug, Inc.*, the defendant drug company promoted the use of its drug for the treatment of lupus, an indication that had not been approved by the FDA. 485 F.2d 132, 138 (3d Cir. 1973). In *Toole v. Richardson-Merrell, Inc.*, the drug company's submission of false and

misleading reports to the FDA gave rise to a "presumption of negligence". 251 Cal.App. 2d 689, 702-04 (Cal. App. 1967). And, in a number of cases, courts have held that overpromotion of a drug by the manufacturer may have undermined the effectiveness of its label warnings and created a triable issue regarding negligence. *See, e.g., Whitley v. Cubberly*, 210 S.E.2d 289, 291-92 (N.C. App. 1974); *Stevens v. Parke, Davis & Co.*, 507 P.2d at 662; *Incollingo v. Ewing*, 282 A.2d 206, 220 (Pa. 1971); *Love v. Wolf*, 226 Cal. App. 2d 378, 396 (Cal. Ct. App. 1964).

Respondent Diana Levine offered comparable evidence at trial. She introduced evidence that, although the FDA was concerned about the greater dangers of inadvertent arterial exposure associated with intravenous (IV) administration of Phenergan, as opposed to intramuscular administration, the agency never directly considered or addressed the relative merits of IV push versus IV drip as methods of IV administration. *See* Pet. App. 167a-168a (Phenergan label); Resp. Br. at 10-14. In addition, plaintiff presented expert testimony at trial that Pfizer, the manufacturer of Vistaril, a product posing risks similar to Phenergan when administered intravenously, voluntarily modified its label around 1970 to permit only intramuscular administration and to prohibit IV use. Trial Tr., Mar. 8, 2004, Vol. I, at pp. 232-33 (testimony of Dr. Harold Green). This was more than sufficient evidence for a jury to decide that Wyeth should have "take[n] additional precautions."

Thus, since long before there was any federal regulation of prescription drugs, the legal principle has been well established that compliance with

regulatory requirements does not preclude a finding of negligence. And that has remained the predominant common law rule, through each revision of federal food and drug law, without objection from Congress or, until recently, the FDA.

B. Virtually Every State, and the Congress, Have Declined to Treat Regulatory Compliance as Conclusive of Non-Negligence.

As the administrative state—including the federal regulation of prescription drugs—has grown more comprehensive and complex, some have asserted that this traditional common law treatment of regulatory compliance was insufficient and have argued for a strengthened regulatory compliance defense that would, under certain circumstances, preclude a finding of liability. *See, e.g.*, Peter Huber, *Safety and the Second Best: The Hazards of Public Risk Management in the Courts*, 85 Colum. L. Rev. 277 (1985); Richard A. Epstein, *Legal Liability for Medical Innovation*, 8 Cardozo L.Rev. 1139 (1987). Despite this advocacy, virtually every state, as well as the Congress, has declined to make regulatory compliance a dispositive affirmative defense.

Many state legislatures have considered whether to adopt a regulatory compliance affirmative defense, but only one—the state of Michigan—has actually done so.[4] A handful of states have passed laws that

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[4] Michigan, alone among the states, has determined that compliance with FDA labeling requirements should bar virtually any liability for failure to warn. Mich. Comp. Laws Ann. § 600.2946(5) provides that a drug "is not defective or unreasonably dangerous, and the manufacturer or seller is not liable, if the drug was approved for safety and efficacy by the

create a presumption that a defendant who satisfies regulatory requirements is not negligent, but make that presumption rebuttable.[5] Such statutes do not depart much, if at all, from the common law rule: a plaintiff may still rebut the presumption by presenting evidence that, under the circumstances, a reasonable defendant would have gone further.

A smaller number of states have decided that compliance with FDA requirements should be a bar to punitive damages, absent a showing that the defendant defrauded or withheld information from the agency.[6] These statutes, however, do not limit a

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[FDA], and the drug and its labeling were in compliance with the [FDA's] approval at the time the drug left the control of the manufacturer or seller." The statute does leave open the possibility that a drug company may be liable if it withheld or misrepresented information that it was required to submit to the FDA, *id.* § 600.2946(5)(a), though courts have divided about whether this so-called "fraud" exception is preempted under this Court's decision in *Buckman Co. v. Plaintiff's Legal Committee*, 531 U.S. 341 (2001). *Compare Garcia v. Wyeth-Ayerst Labs.*, 385 F.3d 961 (6th Cir. 2004), *with DeSiano v. Warner-Lambert & Co.*, 467 F.3d 85 (2d Cir. 2006), *aff'd by equally divided court sub nom. Warner-Lambert Co., LLC v. Kent*, 128 S.Ct. 1168 (2008).

[5] *See* Colo. Rev. Stat. § 13-21-403 (1)(b); Ind. Code Ann. § 34-20-5-1; Kan. Stat. Ann. § 60-3304; Ky. Rev. Stat. Ann. § 411.310(2); Tenn. Code Ann. § 29-28-104; Utah Code Ann. § 78B-6-703(2). New Jersey and Texas also create such a rebuttable presumption specifically for FDA-approved warnings. *See* N.J. Stat. Ann. § 2A:58C-4; Tex. Civ. Prac. & Rem. Code Ann. § 82.007.

[6] *See* Ariz. Rev. Stat. Ann. § 12-701; N.J. Stat. Ann. § 2A:58C-5(c); Ohio Rev. Code Ann. § 2307.80(C)(1); Or. Rev. Stat. § 30.927; Utah Code Ann. § 78B-8-203; *cf.* Colo. Rev. Stat. § 13-64-302.5(5)(a) (limiting protection against punitive damages to health care professionals).

drug company defendant's exposure to compensatory damages if a jury finds fault with its conduct.

Thus, even after careful legislative consideration, forty-nine of the fifty states have rejected a regulatory compliance affirmative defense to liability for failure to warn of the dangers posed by prescription drugs.

Congress has been even less willing to treat federal regulatory compliance as a barrier to state tort liability. In 1977, legislation was proposed in the Senate that would have given manufacturers a defense to damage claims if they complied with federal product safety standards, S. 403, 95th Cong., 1st Sess. § 601 (1977), but no action was taken on it. That same year, a bill introduced in the House would have created a rebuttable presumption that a product that complied with applicable standards was not negligently or defectively designed, H.R. 6300, 95th Cong., 1st Sess. § 8(a)(3), but no action was taken. Similar bills, H.R. 5626 and H.R. 7284, introduced in 1979 and 1982 respectively, met the same fate.

In the 1980s and early 1990s, a number of bills were introduced that would have established a regulatory compliance defense to punitive damages, sometimes limited to drug and device companies and airplane manufacturers, but which would not have affected compensatory damage claims. *See, e.g.*, S. 1999, 99th Cong., 1st Sess. § 306(c) (1985); S. 2760, 99th Cong., 2nd Sess. § 303(c)(1) (1986); S. 640, 102d Cong., 1st Sess. § 303(c) (1991); S. 687, 103d Cong., 1st Sess. § 203(b)(1) (1993). While several of these bills made it to the Senate floor, none was passed. *See generally*, Richard C. Ausness, *The Case for a*

"Strong" Regulatory Compliance Defense, 55 Md. L. Rev. 1210, 1248-51 (1996). The House of Representatives did once adopt a provision immunizing drug companies from punitive damages for FDA-approved drugs as part of sweeping tort reform legislation, H.R. 956, 104th Cong., 1st Sess. § 201(f) (as passed by House, Mar. 10, 1995), but that provision was dropped in conference to avoid likely rejection in the Senate, and the bill was vetoed by President Clinton. *See* Teresa Moran Schwartz, *Regulatory Standards and Products Liability: Striking the Right Balance Between the Two,* 30 U. Mich. J.L. Ref. 431, 441 n.50 (1997) ("*Striking the Right Balance*").

Thus, despite numerous opportunities to consider the issue, Congress has been unwilling to enact even the more limited restrictions on state tort liability—the rebuttable presumption and bar to punitive damages—that have been adopted by some states. Congress has shown no interest whatsoever in going further and making compliance with FDA regulations a complete defense to liability for failure to warn.

C. An FDA Compliance Defense Would Pose Many Problems.

Congress and the states had good reason for rejecting a regulatory compliance defense for prescription drugs. Such a defense would necessarily be narrow and difficult to apply, would place excessive reliance on an underfinanced FDA for drug safety, would undermine incentives for manufacturers to apply to the FDA to strengthen their label warnings, would—if effected by the federal government—infringe upon state

sovereignty, and would leave persons injured by drugs with inadequate warnings without any remedy for their injuries. *See generally,* Michael D. Green, *Statutory Compliance and Tort Liability: Examining the Strongest Case,* 30 U. Mich. J.L. Ref. 461 (1997); Schwartz, *supra, Striking the Right Balance,* 30 U. Mich. J.L. Ref. 431; Robert L. Rabin, *Reassessing Regulatory Compliance,* 88 Geo. L.J. 2049 (2000).

Such an affirmative defense would be narrow and difficult to apply for many reasons. First, courts would have to determine whether the precise question in the underlying tort litigation had been considered and resolved by the FDA. Teresa Moran Schwartz, *The Role of Federal Safety Regulations In Products Liability Actions,* 41 Vand. L. Rev. 1121, 1130-31 (1988) ("If an agency has not addressed specifically the matter before the court, the argument for judicial deference fails."). Next, defendants would have to demonstrate not simply that their drug and label had been approved by the FDA, but also that they had complied with all regulatory requirements regarding both pre-approval testing and post-approval marketing, to ensure that the agency had all necessary information when rendering its judgment; this would significantly limit the defense's utility as a tool to simplify tort litigation. Green, 30 U. Mich. J.L. Ref. at 481-82, 488-90. Moreover, an FDA compliance defense would have virtually no applicability to the majority of failure-to-warn cases, which involve risks discovered after product approval,[7] off-label uses,[8] or

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[7] Most failure-to-warn cases involve "risks that emerged after the drugs were approved by the FDA and made available to the public." *Id.* at 473; *see also* GAO, *FDA Drug Review: Post-Approval Risks 1976-85* 3 (1990) (over half of approved drugs had serious risks not detected until after FDA approval).

allegations of overpromotion, all contexts in which the FDA cannot have weighed the optimal balance between over- and under-warning. Rabin, 88 Geo. L. Rev. at 2077-82.

A compliance defense would also place excessive reliance on the FDA. Even if the agency had adequate resources, there would be problems of regulatory obsolescence and regulatory lag, the time it takes for the FDA to process and act upon new information. Moreover, the agency is dependent on drug companies for information and such companies have substantial influence upon the drug approval process. And, report after report in recent years has concluded that the FDA is under-resourced and under-staffed to ensure the currency and adequacy of existing drug labels. *See,* Schwartz, *Striking the Right Balance,* 30 U. Mich. J.L. Ref. at 443-46; IOM Report, *supra,* 197-98; *Mission at Risk, supra,* 2-3.

Third, a regulatory compliance defense would have a negative effect on the adequacy of FDA labeling requirements; a defense to tort liability would give drug companies strong incentives to resist efforts to strengthen the warnings on their products. Schwartz, *Striking the Right Balance,* 30

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[6] Estimates are that close to half of all American drug prescriptions are written for indications that have not been approved by the FDA. *See* Kaspar J. Stoffelmayr, *Products Liability and "Off-Label" Uses of Prescription Drugs,* 63 U. Chi. L. Rev. 275, 278 (1996). As the agency has observed: "Once a drug product has been approved for marketing, a physician may, in treating patients, prescribe the drug for uses not included in the drug's approved labeling. The primary legal constraints in that situation are State laws on medical practice and *products liability law.*" 48 Fed. Reg. 26,720, 26,733 (June 9, 1983) (emphasis added).

U. Mich. J.L. Ref. at 452-53; Green, 30 U. Mich. J.L. Ref. at 501-02.

Fourth, displacement of state tort law by the federal government would be a significant infringement on state sovereignty. As this Court has acknowledged repeatedly, "regulation of health and safety matters is primarily, and historically, a matter of local concern," within the police powers of the states. *Hillsborough Cty. v. Automated Med. Labs., Inc.*, 471 U.S. 707, 719 (1982). The states have experimented with various approaches to address the relationship between regulatory compliance and tort law.[9] To override the states' ability to define that relationship in their civil justice systems would deprive states of their autonomy and do serious harm to our federalism. Rabin, 88 Geo. L. Rev. at 2057, 2073-74.

Finally, and most importantly, a regulatory compliance defense would leave those persons injured by drug products, such as Diana Levine, remediless, regardless of the negligence of the drugmaker or the inadequacy of the warnings that had been approved by the FDA. *Id.* at 2073.

Given all these problems, "it is not so surprising that the regulatory compliance defense has never captured the widespread assent of courts and

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[9] In Justice Brandeis' famous words: "It is one of the happy incidents of the federal system that a single courageous state may, if its citizens choose, serve as a laboratory; and try novel social and economic experiments without risk to the rest of the country." *New State Ice Co. v. Liebmann*, 285 U.S. 262, 311 (1932) (Brandeis, J., dissenting).

commentators," *id.* at 2084, or of state legislatures and the Congress.

III. Because State Tort Law Takes Appropriate Account of Compliance with FDA Labeling Requirements, There Can Be No "Direct and Positive Conflict" Between State and Federal Law That Would Justify Preemption.

Wyeth and its *amici*, including the FDA, now seek from this Court what they have been unable to gain from state courts, state legislatures, and the Congress: a broad and blunt regulatory compliance affirmative defense under the guise of implied conflict preemption. Forty-nine of the fifty states have rejected the call for such a defense. They have found state tort law and federal regulation to be complementary systems that can comfortably co-exist. Likewise, Congress has shown no interest in adopting a national compliance affirmative defense, nor has it expressed any intention to preempt state tort remedies against drug companies. To the contrary, Congress has made clear its position that there should be no preemption of state law, except in cases of "direct and positive conflict."

There is no such conflict here. Under the traditional, common law treatment of regulatory compliance, a person injured by a prescription drug will not prevail on a failure-to-warn claim against a drug company that complied with its FDA labeling obligations, unless she can come forward, as Diana Levine did, with evidence that under the circumstances a reasonable drug company would have done more to warn of the dangers posed by its

product. Where such special circumstances exist, a determination of state tort liability against the company cannot be said to be in "direct and positive conflict" with FDA labeling determinations.

CONCLUSION

For the foregoing reasons, *amicus curiae* the American Association for Justice urges this Court to affirm the judgment of the Vermont Supreme Court.

Respectfully Submitted,

August 14, 2008

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Supreme Court of the United States

WYETH,

Petitioner,

v.

DIANA LEVINE,

Respondent.

ON WRIT OF CERTIORARI TO THE SUPREME COURT OF VERMONT

BRIEF OF *AMICI CURIAE* ANJU BUDHWANI, M.D.; CURT D. FURBERG, M.D., PH.D.; ARTHUR AARON LEVIN, M.P.H.; RAHUL SHARMA, M.D., M.B.A.; CANTON ELECTRICAL WELFARE FUND OF THE IBEW, LOCAL 540; HEALTH & WELFARE FUND OF THE DEA, NYPD; RETIREE HEALTH & WELFARE FUND OF THE DEA, NYPD; AND OHIO CARPENTERS HEALTH FUND IN SUPPORT OF RESPONDENT

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INTEREST OF AMICI CURIAE [1]

Healthcare Amici are health care providers, educators, and public health advocates. Their professional responsibilities require that they balance the risks of various pharmaceuticals against their therapeutic benefit, and that they assess the impact of the conduct of the pharmaceutical industry on public health. Amici have a professional interest in ensuring that the public health is protected through laws and public policies.

Third-Party Payor Amici are self-insured union health plan funds, each of which is administered by trustees. The trustees collectively manage an aggregate $61 million in plan assets that are used to provide health insurance and pharmaceutical benefits for over 62,000 current and former union members and their beneficiaries. As health insurers, amici ultimately provide coverage when plan participants experience adverse reactions to their medication. If these reactions can be shown to have been caused by a manufacturer's failure to warn of foreseeable risks, amici have the right to recoup their costs by exercising subrogation and reimbursement rights. These provisions are critical cost-saving measures in the face of rapidly increasing healthcare prices, and help self-insured plans keep down

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[1] No counsel for a party authored this brief in whole or in part, and no such counsel or party made a monetary contribution intended to fund the preparation or submission of this brief. No person other than the *amici curiae*, or their counsel, made a monetary contribution to its preparation or submission. The parties have filed waivers consenting to the filing of all *amicus* briefs.

health insurance costs. The matters under review by this Court directly affect amici's ability to recoup expenses associated with unreasonably unsafe medication.

SUMMARY OF ARGUMENT

Phenergan, the brand name for the generic compound promethazine hydrochloride, was approved for sale in 1955. Phenergan has a low "pH," meaning that it is acidic and highly damaging to human tissue. At the time the Food and Drug Administration ("FDA") approved Wyeth's new drug application, safety reviews were far more cursory than they are today, and they did not involve "balancing" a drug's risks against its expected benefits. In the years following Phenergan's approval, FDA reviews of the drug were of limited scope, and there is no evidence that Wyeth ever submitted, or that FDA considered, comprehensive analyses of the frequency and severity of injuries associated with Phenergan.

Intravenous medications like promethazine may be administered by IV push or IV drip. IV push administration is more likely to result in "extravasation," the inadvertent administration of medication outside the vein and into surrounding tissues. Because extravasation is not rare, the medical profession classifies drugs by their potential to cause injury if they extravasate. Most drugs are relatively safe, and extravasation is not serious. Some drugs, like promethazine, are classified as "irritants." Irritants cause pain and swelling when they extravasate, but do not usually cause permanent damage. The most dangerous drugs, classified as "vesicants," can cause tissue necrosis and gangrene, among other serious injuries. Hospitals create special policies for the administration of

vesicants, including, in some instances, limitations on IV push administration. As an irritant, however, promethazine has not been subject to these policies; promethazine has usually been administered by nurses via IV push, with none of the precautions associated with vesicants. Only recently have the dangers of promethazine been publicized, and FDA has now twice posted warnings about IV administration of promethazine on its website, identifying it as a "known vesicant" despite its labeling.

Although there are few published reports of injuries caused by promethazine, it is possible to analyze individual reports of injuries in the FDA's database. This analysis demonstrates that between November 1997 and December 2006, reported injuries associated with promethazine were thirty times more likely to involve gangrene or amputation than injuries associated with other intravenous drugs. Yet there is no evidence that Wyeth ever conducted an analysis of the frequency of these injuries, or submitted an analysis to FDA.

The story of Phenergan thus serves as a cautionary tale of how insufficient manufacturer vigilance, coupled with lax regulatory oversight, can cause serious injuries to patients. Nor is Phenergan an isolated example. On average, 1.5 drugs per year were withdrawn over safety concerns between 1993 and 2006. Anecdotal reports of particular drugs withdrawn from the market – for safety problems foreseeable years earlier – suggest that unreasonably unsafe medication causes large numbers of fatalities, and that associated costs can run into billions of dollars. As many as 30% of hospitalized patients may experience an adverse drug event, and such patients are likely to see costs increase by $1,900 to $7,000.

These costs are ordinarily borne by patients and their insurers. However, when an adverse drug reaction is caused by the manufacturer's failure to warn of foreseeable risks, third party payors' reimbursement and subrogation rights can serve as a powerful cost-containment mechanism that helps keep down health insurance costs. If this Court holds that state tort claims are preempted by FDA regulations, neither patients nor insurers will be able to shift the costs of injuries to the drug manufacturers who, with their superior information about, and control over, their products, are in the best position to avoid them. Ultimately, all consumers will pay the price in higher costs for basic healthcare.

ARGUMENT

I. PHENERGAN AND INTRAVENOUS ADMINISTRATION

A. Phenergan and its History with FDA

Phenergan is the brand name for promethazine hydrochloride, a compound first synthesized in 1946. *See* B.N. Halpern & R. Ducrot, *Experimental Research on a New Series of Chemical Substitutes with Powerful Antihistaminic Activities: The Phenothiazine Derivatives*, 140 Comp. Rend. Soc. Biol. 361 (1946) *(Fr.)*. Promethazine belongs to a class of drugs known as "H1 blockers," which means that it is an antihistamine that operates by blocking the ability of the body's neurons to respond to the presence of the neurotransmitter histamine. *See* Chiaki Kamei & Kenji Tasaka, *Participation of Histamine in the Step-Through Active Avoidance Response and its Inhibition by*

H1-Blockers, 57 Japanese J. Pharmacology 473 (1991); Troy E. Brown & Dwain L. Eckberg, *Promethazine Affects Autonomic Cardiovascular Mechanisms Minimally*, 282 J. Pharmacology & Experimental Therapeutics 839 (1997). Promethazine also acts as a D2 and M1 blocker, meaning that it blocks neurons from responding to the neurotransmitters dopamine and acetylcholine. By blocking histamine, dopamine, and acetylcholine, promethazine can prevent these neurotransmitters from exerting various effects, such as activating the brain areas that control vomiting and nausea. *See* Julie Golembiewski & Sheri Tokumaru, *Pharmacological Prophylaxis and Management of Adult Postoperative/Postdischarge Nausea and Vomiting*, 21 J. PeriAnesthesia Nursing 385 (2006). Promethazine is thus used to treat, among other things, allergic reactions, nausea, and motion-sickness. *See* JA390.

Promethazine is available in tablets, suppositories, and cough syrup, in addition to the injectable form at issue here. In its injectable form, promethazine has a pH of 4 to 5.5. JA390. pH, or "potential of hydrogen," is a 0 to 14 scale that measures the acidity or alkalinity of a solution. Water, a neutral solution, has a pH of 7. Human body fluids typically have a pH of around 7.4. *See* Sharon M. Weinstein, *Plumer's Principles & Practice of Intravenous Therapy* 99-100 (8th ed. 2007). Promethazine, with its low pH, is, essentially, an acid, and also contains an additional irritating substance, which is why it can cause such damage. *See* JA94; Susan Paparella, *The Dangers of Intravenous Promethazine Administration*, 33 J. Emergency Nursing 53, 54 (2007). In worst case scenarios, Phenergan damages an

artery, cutting off blood flow to the surrounding areas, with resulting tissue necrosis, gangrene, and, ultimately, amputation. JA72. In other cases, Phenergan may not reach an artery, but may still cause very serious injuries, such as nerve damage, phlebitis and thrombophlebitis (vein inflammation and inflammation with clotting), abscesses, and tissue necrosis, requiring skin grafts and fasciotomy (cutting of connective tissue). *See* Baxter Pharm., *Phenergan Injection* ("Baxter Label") (2005), htttp://www.baxter.com/products/anesthesia/anesthetic_pharmaceuticals/downloads/ phenergan.pdf (listing injuries that can occur "regardless of the route of administration").[2]

Phenergan was first approved for sale in its injectable form in 1955. JA266-67. At that time, prior to the 1962 Kefauver-Harris Amendments to the Food, Drug, & Cosmetic Act ("FDCA"), FDA was empowered to review drugs for safety but not efficacy. *See* FDCA, Pub. L. No. 75-717, § 505, 52 Stat. 1040, 1052 (1938). If FDA took no action within 180 days of a new drug application, the application would automatically become effective. *Id.* There was no review to determine whether the drug was efficacious for its intended uses, and thus, necessarily, there was no balancing of risks relative to benefits. The safety reviews of that time were far more cursory than those conducted today; only after the 1962 amendments were more stringent requirements enacted, such as the requirement that manufacturers conduct well-controlled trials in three phases. *See* Katherine A. Helm, *Protecting Public Health From*

[2] In 2002, Baxter Healthcare Corporation acquired the division of Wyeth that manufactured the injectable form of Phenergan; the labeling was subsequently revised.

Outside the Physician's Office, 18 Fordham Intell. Prop. Media & Ent. L.J. 117, 129 (2007). Though the 1962 amendments still allowed for automatic approval if FDA took no action, in practice, after 1962, FDA routinely requested additional information within the prescribed period, thus delaying approval substantially. *Id.* at 130 n.40.

As a result of the pre-1962 system, not only did Phenergan receive a less stringent safety review than would have occurred today, but there is no evidence that FDA considered the risks of intravenous relative to intramuscular administration, let alone the distinction between IV drip and IV push. At around the time of FDA's approval, published studies of Phenergan typically did not compare the safety of different forms of administration (oral, intramuscular, intravenous), nor did they distinguish between IV push and IV drip. *E.g.*, Geraldine Light, et al, *Promethazine (Phenergan) as an Adjunct to Anesthesia*, 164 JAMA 1648 (1957); Max Sadove, *Promethazine in Surgery*, 162 JAMA 712 (1956); R.W. Baxter, et al., *Three Phenothiazine Derivatives in Anesthesia*, 9 Anaesthesia 79 (1954). Wyeth did not introduce any evidence at trial suggesting that it supplied FDA with comparisons of the safety of various modes of administration. Thus, there is no reason to believe that any such studies were presented to FDA prior to Phenergan's approval.

There is similarly no reason to believe that Phenergan's safety was revisited by FDA after the 1962 FDCA amendments. With these amendments, Congress directed FDA to review the efficacy, as well as the safety, of new drugs. *See* S. Rep. No. 87-1744, at 9-10 (1962).

The new statutory provisions required FDA to determine whether drugs that had been approved between 1938 and 1962 – and thus had never been reviewed for efficacy – were effective for their indications. *See* Pub. L. No. 87-781, §107, 76 Stat. 780, 788-89 (1962). At the time of the Act's passage, FDA had fewer than a dozen physicians on staff and thus could not make efficacy determinations on its own; instead, it contracted with the National Academy of Sciences ("NAS") to conduct the reviews in a program that would be known as the Drug Efficacy Study Implementation ("DESI") Review. *See* Erika Lietzan, *Advisory Committees at FDA*, 39 J. Health L. 415, 420 (2006). FDA directed that all holders of new drug applications approved between 1938 and 1962 submit to the NAS various types of information, including a "[l]ist of literature references most pertinent to an evaluation of the effectiveness of the drug for the purposes for which it is offered in the label, package insert, or brochure," as well as unpublished articles on the same topic. 31 Fed. Reg. 9426, 9426 (1966).

To conduct the reviews, "[t]he NAS, not FDA, selected the experts who served on the [DESI] panels. Meetings were closed to the public, and indeed to FDA, and neither the date nor the location was announced in advance." Lietzan, *supra*, at 420 n.18. If the drug was evaluated as effective, the manufacturer supplied FDA with an amended label, after which time "new-drug applications which became effective on the basis of safety prior to October 10, 1962, will be approved on the basis of effectiveness as well as safety of the drug." 35 Fed. Reg. 11,273, 11,273 (1970). Thus, nothing in the DESI program — or the record in this case — suggests

that FDA had any reason to revisit Phenergan's safety as part of the post-1962 drug reevaluations.[3]

In the mid-1970s, FDA requested revisions to Phenergan's labeling, including to the warnings concerning intra-arterial injection. JA270-296. However, once again, there is no evidence that Wyeth supplied FDA with any studies or analyses concerning the frequency or severity of injuries associated with intravenous administration generally, or specifically comparing injury rates of IV push and IV drip.

In 1980, FDA initiated its Labeling Format Revision Program. *See* 45 Fed. Reg. 32,550 (1980). At that time, the Phenergan label contained almost the same language concerning intra-arterial administration that would exist on the 2000 label at the time of Respondent's injuries. *Compare* Phenergan Injection, in *Physicians' Desk Reference* 1946-48 (35th ed. 1981) *with* JA390. Wyeth submitted a supplemental application to conform its label to the new format in 1981, and over a period of 17 years, Wyeth and FDA intermittently exchanged correspondence on the subject. JA297-354. During this process, FDA requested revisions to the warnings regarding inadvertent intra-arterial administration. JA309-19. Correspondence sometimes halted for years and, on at least two occasions, FDA apparently lost track of the status of Wyeth's labeling and application. JA347; JA353 (Wyeth supplies FDA with "administrative

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[3] DESI took years to complete. Approximately 20 drugs approved between 1938 and 1962 remain on the market today without a final determination of effectiveness. *See* Peter Barton Hutt, *The State of Science at the Food and Drug Administration*, 60 Admin. L. Rev. 431, 447 (2008).

record" of Wyeth's supplemental application; Wyeth provides FDA with "narrative" comparing 1992 and 1996 labels).

Finally, in February 1997, FDA approved Wyeth's supplemental application conditioned on Wyeth further amending the draft label. JA357. Regarding inadvertent intra-arterial injection, the letter stated "Retain verbiage in current label," an apparent reference to the language on the 1996 label that had existed unchanged since at least 1980. JA359. No reference was made to earlier reviewers' requests for amendments, and no reasons were offered for FDA's reversal, although the United States now offers that FDA believed its earlier changes to be "non-substantive." U.S. Br. 25. Wyeth submitted a new label in 1998, and later that year, FDA completed its review. JA382. There is no evidence in the record suggesting that during this 17-year-process, Wyeth ever supplied FDA with any analysis or review of Phenergan's safety profile, nor is there evidence that FDA requested or reviewed such data.

Thus, given the cursory requirements of the 1938 regime, the limited scope of the DESI program, and a labeling review process that did not apparently involve any quantitative examinations of Phenergan's safety, nothing in the record suggests that Wyeth ever submitted to FDA comprehensive analyses concerning the safety of the injectable form of Phenergan – or concerning the frequency or severity of injuries associated with intravenous administration – at any time in Phenergan's 53-year history.

B. Procedures for Intravenous Administration; Classification of Phenergan as an "Irritant"

In most intravenous administrations, the clinician uses a metal needle covered by a plastic sheath, or catheter, to pierce the vein. The needle is removed, leaving the catheter partly buried within the vein. *See* Weinstein, *supra*, at 221. The infusion set, a length of flexible tubing ("line"), connects the catheter to a fluid container, such as a plastic bag or syringe. *See id.* at 224-225, 267. Medication can be administered through the infusion set via "IV drip," or can be injected into the vein via "IV push." IV push administration can be accomplished by injecting the drug into the infusion set or tubing, or into the catheter. *See* Weinstein, *supra*, at 479. For some medications, the clinician may choose to use a butterfly infusion set, where medication is delivered through tubing attached to a needle, rather than through a catheter. JA46-48.

Before needle insertion, the clinician decides whether to use a peripheral vein or a central vein. Peripheral veins are located in the extremities, and most IV medications are administered through the veins of the hands and arms. *See* Teresa Finlay, *Intravenous Therapy* 38 (2004). Central veins are located in the neck and chest cavity. *Id.* at 40-41. Peripheral vein infusion is a task performed by registered nurses. *See* Weinstein, *supra*, at 7-8. Central venous administration, by contrast, must be ordered by a physician, and under many state regulations (and/or hospital policies), nurses may not insert central lines. *Id.* at 289; *see* Md. Regs. Code tit. 10, §.27.20.06 (nurses with special training may remove, but not place, central catheters);

Conn. Agencies Regs. §19-13-D72 (nurses may only insert central catheters placed through a peripheral vein, and only with special training).

One of the risks associated with IV administration is "extravasation," or inadvertent administration of medication outside the vein and into surrounding tissues. *See* Carmel Sauerland et al., *Vesicant Extravasation Part I*, 33 Oncology Nursing F. 1134 (2006). There are many reasons a drug might extravasate, such as improper needle placement or dislodgment of the catheter or needle. *E.g.*, JA67, 70-71. Extravasation is less likely to occur during IV drip because improper catheter placement halts the flow of IV drip fluid, alerting the clinician. Additionally, the needle of the winged infusion set often used for IV push is more likely to become dislodged or damage the vein than would the soft catheter typically used in IV drip. JA67-71; *see* John R. Keene, et al, *Accidental Intra-arterial Injection: A Case Report, New Treatment Modalities, and a Review of the Literature*, 64 J. Oral and Maxiollofacial Surgery 965, 967 (2006) (recommending IV drip to avoid extravasation).

Because extravasation is not uncommon, JA73, 75-76; Weinstein, *supra*, at 154, the medical profession classifies intravenous drugs by their potential to cause injury. Most drugs are relatively harmless, and extravasation is not a serious event. *See* Weinstein, *supra*, at 154. Some drugs, classified as "irritants," may cause inflammation and pain, but do not result in tissue necrosis or long-term damage. "Vesicant" drugs, however, may cause tissue necrosis, gangrene, and severe or permanent injuries. *See* Aimee S. Payne et

al., *Chemotherapy Extravasation Injury*, UpToDate (Sept. 2007), http://www.uptodate.com/home/index.html; Sauerland, *supra*, at 1134-35.[4] Although the distinction between vesicants and irritants is not always a bright line,[5] extravasation of drugs classified as vesicants in particular is a "medical emergency." Elizabeth Kassner, *Evaluation and Treatment of Chemotherapy Extravasation Injuries*, 17 J. Pediatric Oncology Nursing 135, 139 (2000).[6]

Consequently, clinicians are instructed to take special precautions when administering drugs classified as vesicants. For example, one common recommendation is that vesicants be administered through central veins, because central veins' larger size makes extravasation less likely.[7] *See* Finlay, *supra*, at 42, 75; Sauerland, *supra*,

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[4] UpToDate is an online medical research database that is commonly used as a basic reference guide by physicians

[5] Some irritants may occasionally be associated with tissue destruction. As Payne explains, "As an example, there is one case report of tissue necrosis from an extravasation of oxaliplatin, although another series of 11 patients showed no tissue destruction. In such cases, the extent of tissue injury may be a function of the amount of drug extravasated." Payne, *supra*; *see* Sauerland, *supra*, at 1135 (reporting that the irritant Cisplatin has vesicant potential if it extravasates in large quantities).

[6] Vesicants are commonly associated with chemotherapy, and are often discussed in the oncology context, where the risks and benefits of administration may differ from other contexts.

[7] By contrast, one author recommends central venous administration for irritants only if the infusion will be "continuous," *see* Finlay, *supra*, at 75, which, in medical jargon, means a period exceeding two hours, *see* Weinstein, *supra*, at 479.

at 1139 (describing central IV as the "preferred route of administration" for vesicants). Clinicians are sometimes instructed to use plastic needles, because metal can damage veins. *See* Sauerland, *supra*, at 1136. Some hospitals limit who may administer vesicants and by what method. *See, e.g.*, University of New Mexico Hospitals, *Chemotherapy* (July 2000), http://hospitals.unm.edu/policies_and_procedures/ (select Pharmacy, Chemotherapy) (vesicants may only be administered by central lines; IV push of vesicants via peripheral line only permissible by an oncology-certified nurse); Cincinnati Children's Hospital Medical Center, *Vesicant Chemotherapy Extravasation* (June 2003), http://www.cincinnatichildrens.org/ed/cme/ed-services/policies.htm (special training required to administer vesicants). Clinicians are directed not to administer vesicants in the antecubital region at the bend of the elbow – the site used for Respondent's IV infusion, JA69-70 – because the needle or catheter can easily become dislodged, and because the proximity to arteries heightens the risk of serious injury. *See* Sauerland, *supra*, at 1136; Cincinnati Children's Hospital, *supra*. Clinicians may be discouraged from using veins in the hand and wrist for similar reasons. *See* Sauerland, *supra*, at 1136-37. Indeed, the dangers of extravasation are so closely identified with vesicants that the Oregon Board of Nursing defines extravasation only to mean "[i]nadvertent infiltration of vesicant solution or medication into surrounding tissue." Oregon State Board of Nursing, *Advisory Guidelines for Infusion Therapy* (Sept. 20, 2001), http://www.oregon.gov/OSBN/pdfs/policies/infusion2.pdf. In sum, though specific policies on administration of irritants and vesicants vary, clinicians regard the distinction between vesicants and

other drugs as significant, and modulate precautions accordingly.

Phenergan is not identified as a vesicant on its labeling. Instead, Phenergan labeling identifies it as a "known arteriolar irritant," and provides instructions for "administering any irritant drug intravenously." JA390. In practice, as an irritant, promethazine is usually administered via IV push through peripheral, rather than central, veins. *See* Institute for Safe Medication Practices ("ISMP"), *Action Needed to Prevent Serious Tissue Injury with IV Promethazine* (Aug. 10, 2006) ("*Action Needed*"), http://www.ismp.org/newsletters/acutecare/articles/20060810.asp; ISMP, *Promethazine Conundrum: IV Can Hurt More than IM Injection!* (Nov. 2, 2006) ("*Promethazine Conundrum*"), http://www.ismp.org/newsletters/acutecare/articles/20061102.asp; Paparella, *supra*, at 54-55. In fact, after ISMP referred to promethazine as a "known vesicant" in its August 2006 issue, it was forced to retract that characterization after readers pointed out that the labeling referred to promethazine as only an irritant. *See Promethazine Conundrum*, *supra*.

Thus, until recently, the dangers posed by Phenergan were not commonly known among clinicians. *See* Paparella, *supra*, at 55. As of 2006, there were few published reports of inadvertent intra-arterial injection or extravasation. *See* Keene, *supra*, at 966; Mark A. Malesker et al., *Extravasation of I.V. Promethazine*, 56 Am. J. Health-Sys. Pharmacy 1742 (1999) ("[A] search of the primary literature . . . produced no reports of extravasation of promethazine. Similarly, the manufacturer was unable to provide references to

published reports."). Paparella writes that "[e]mergency department nurses are asked frequently to give this medication intravenous push, yet many are unaware of the risks associated with this practice and the serious outcomes that may occur with intravenous administration." Paparella, *supra*, at 55. One nurse observed that nurses were "casual" about how they delivered promethazine intravenously. *See* Susan Hohenhaus, *An Informal Discussion of Emergency Nurses' Current Clinical Practice*, 31 J. Emergency Nursing 465 (2005). But though few reports had been published, in August 2006, ISMP reported its own analysis of individual accounts from different sources, concluding that "scores" of unpublished reports indicated that "patient harm may be occurring more frequently than recognized." *Action Needed*, *supra*; *see Promethazine Conundrum*, *supra* ("Promethazine extravasations that result in serious tissue damage are not rare; indeed, one in five respondents reported awareness of such an occurrence in their facility within the past 5 years.").[8]

In recent years, the dangers of promethazine have become publicized. The ISMP issued a warning about intravenous administration in August 2006, and pointed out that newer drugs such as Zofran, which did not exist when Phenergan was approved for sale, are safer than promethazine. The ISMP recommended that promethazine be contraindicated for IV use, or that

[8] The Director of the FDA Office of Pharmacoepidemiology and Statistical Science described ISMP as "one of most important sources [FDA] has for obtaining information on medication errors occurring in health systems." *ISMP Testimonials*, http://www.ismp.org/about/testimonials.asp.

precautions similar to those taken with vesicants be used (central venous administration, avoid hands and wrists). *See Action Needed, supra*. Some hospitals have labeled promethazine as a vesicant in their own formularies, even though the drug is only formally designated as an irritant. *See Promethazine Conundrum, supra*; Utah University Health Care, *Promethazine (Phenergan) Injection Classified as Vesicant* (Apr. 2005), http://uuhsc.utah.edu/pharmacy/alerts/87.html. In February 2007, the Veterans Health Administration issued a promethazine warning, ordering that local VHA facilities develop protocols for promethazine usage. *See* U.S. Dep't of Veterans Affairs, VHA Pharmacy Benefits Management Strategic Healthcare Group and Medical Advisory Panel, *National PBM Drug Guidance: Promethazine HCL Injection* (Feb. 2007), http://www.pbm.va.gov/VACenterForMedicationSafety-BulletinsAndNewsAlerts.aspx.

Ironically, after ISMP issued its August 2006 report on promethazine's dangers, FDA endorsed ISMP's report and linked to it on its website. *See* FDA, *Preventing Medical Errors: Severe Tissue Injury with IV Promethazine* (Dec. 2006), http://www.accessdata.fda.gov/psn/transcript.cfm?show=58#6. FDA considered ISMP's report so important that in February 2008, it reissued the warning to "repeat[] some of the most important safety issues that continue to pose a public health concern." FDA, *Severe Tissue Injury with IV Promethazine (December 2006)* (Feb. 2008), http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/psn/transcript.cfm?show=72#5. In both notices, FDA reiterated the ISMP's characterization of promethazine as a "known vesicant."

C. Adverse Event Reports in the FDA Database

As ISMP concluded, despite the dearth of published accounts of injuries from promethazine, there are individual reports dating back many years. Wyeth, as manufacturer, was required to forward certain of these reports to FDA. 21 C.F.R. §314.80(c). FDA also receives reports from health care professionals and consumers. *See* Center for Drug Evaluation and Research ("CDER"), *Adverse Event Reporting System* ("AERS") (June 6, 2008), http://www.fda.gov/cder/aers/default.htm. Additionally, Wyeth was obligated to develop procedures "for the surveillance, receipt, evaluation, and reporting" of such injuries to FDA. 21 C.F.R. §314.80(b); *see* CDER, *Guidance for Industry Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment* 3-4 (March 2005) ("CDER Guidance"), http://www.fda.gov/Cder/Guidance/6359OCC.pdf. Despite these obligations, no evidence was introduced at trial to suggest that Wyeth ever presented FDA with any surveillance or evaluation of the injuries caused by extravasation. As it turns out, even the most rudimentary analyses might have revealed the extent of the dangers posed by Phenergan, and triggered closer FDA scrutiny.

"Adverse event" reports submitted to FDA – individual reports of unwanted, negative consequences associated with medication – are publicly available in the AERS database. *See* http://www.fda.gov/cder/aers/default.htm. The database dates back to 1969, and each report identifies the drug, the adverse event, and the method of administration (though they do not distinguish between IV push and IV drip). However,

prior to November 1997, the database employed a medical dictionary called COSTART, which recognized only 1,200 terms. Because terms were so limited, reports were coded in ways that were not always fully descriptive. For example, COSTART did not utilize the term "amputation"; instead, reports of amputation might be coded as "gangrene," if applicable. After November 1997, FDA changed its database to AERS from the older Spontaneous Reporting System and switched to MedDRA, an expanded classification schema containing approximately 20,000 terms. After the adoption of MedDRA, AERS recognized the term "amputation." *See generally* FDA, *MedDRA: Medical Dictionary for Regulatory Activities*, http://www.fda.gov/Medwatch/report/meddra.htm.

Using AERS, the frequency of injuries associated with intravenous administrations of Phenergan (and generic versions) can be examined. In pharmacoepidemiology, one simple way to determine whether a reaction is associated with a particular drug is by calculating the "proportional reporting rate" ("PRR") of the reaction. *See* Brian Strom, *Pharmacoepidemiology* 180-81 (3d ed. 2000); CDER Guidance at 9. The PRR demonstrates whether the adverse reaction under study represents a greater proportion of all adverse reactions for the subject drug than for comparable drugs. To calculate the PRR, the researcher determines the percentage of times the adverse reaction under study has occurred relative to other adverse reactions. This percentage is then compared to the percentage of times the reaction has occurred, relative to other reactions, in other drugs. For example, the researcher may find that out of 10 reported adverse events for a given drug, 5, or 50%,

involve hallucinations. In a comparable drug, the researcher may find that out of 20 adverse events, 5, or 25%, involve hallucinations. The PRR is 50% divided by 25%, or 2. *See* Strom, *supra*, at 180-81. A second calculation, known as the "chi-square," is then performed. Chi-square is a standard statistical measurement that expresses the degree to which two proportions differ from what one would expect given random chance. *See* Stanton A. Glantz, *Primer of Biostatistics* 113-163 (5th ed. 2002).[9] Though many factors may be relevant, a PRR of 2 or more, coupled with a chi-square of 4 or more, is generally considered a "signal" requiring further investigation. *See* Strom, *supra*, at 180-81.

Wyeth, with its access to adverse event data, could easily have performed these basic calculations to compare intravenous promethazine with other intravenous medications and determine whether injuries similar to Respondent's appeared at a high rate. For example, according to AERS, from 1969 through November 1997 (when the database and dictionary changed) there were 307 reported "serious" adverse events associated with promethazine administered

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[9] For example, if two drugs are equally associated with hallucinations, no matter how many adverse event reports are submitted for each drug, the same percentage of each will involve hallucinations. A chi-square is used to measure the extent to which the actual percentages differ from this perfectly equal outcome. Chi-square is defined as "a quantity equal to the summation over all variables of the quotient of the square of the difference between the observed and expected values divided by the expected value of the variable." Random House Webster's Unabridged Dictionary 362 (2d ed. 2001).

intravenously. Of those, 4 (1.30%) were coded as gangrene.[10] During the same period, there were 77,693 reported "serious" adverse events associated with all other medications administered intravenously, with 121 (0.155%) coded as gangrene. Had Wyeth examined this data, it would have calculated a PRR of 8.4 with a chi-square of 25 – a strong signal.

After the adoption of MedDRA, coders could indicate amputations in addition to, or instead of, gangrene. From December 1997 through December 2006, there were 468 serious adverse events associated with intravenous promethazine, of which 11 (2.35%) were coded as gangrene and 20 (4.27%) were coded as amputations. For the same period, 144,346 serious adverse events were reported for all other intravenously-administered medications, of which 111 (0.077%) resulted in gangrene and 213 (0.15%) resulted in amputations.[11] These figures yield a PRR of 30.5 for gangrene and 29 for amputations, with chi-squares of *286* and *494*, respectively – powerful signals of promethazine's dangers.

Additionally, as explained above, promethazine has been associated with injuries besides gangrene and

[10] Because PRR is dependent on voluntary submission of adverse reaction reports, it is inherently vulnerable to underreporting. *See* Phil B. Fontanarosa et al., *Postmarketing Surveillance – Lack of Vigilance, Lack of Trust*, 292 JAMA 2647 (2004); Amalia M. Issa, et al., *Drug Withdrawals in the United States: A Systematic Review of the Evidence and Analysis of Trends*, 2 Current Drug Safety 177, 182-83 (2007).

[11] These data cannot be aggregated; a single patient may experience both gangrene and amputation.

amputation. Several of these are identified in the August 2006 ISMP warning, such as nerve damage, paralysis, phlebitis, and tissue necroses. *See Action Needed, supra.* The MedDRA offers several alternative terms for these reactions and classifies them as related.[12] Had Wyeth analyzed serious adverse events associated with intravenous promethazine between 1969 and November 1997, it would have discovered that 45% (138 of 307) involved reactions related to those in the August ISMP report.[13] By contrast, 13% (10,099 of 77,693) of serious adverse events reported for other intravenous drugs involved reactions related to the ISMP report reactions, for a PRR of 3.46, with a chi-square of 274 — a clear signal of problems with intravenous promethazine.

Expanding the analysis, from 1969 through December 2006, 45.6% (354 out of 775) of the serious adverse event reports for intravenous promethanzine involved reactions related to those listed in the August ISMP report. By contrast, 15.7% (34,905 of 222,039) of serious adverse events reported for other intravenous

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[12] MedDRA is a four-level hierarchical scheme. Terms within the same high-level group are related to one another. For example, "vasculitis," which refers to several different diseases concerning inflammation of the blood vessels, and "phlebitis," are both under the same high level group term "Vascular Inflammations." *See generally* Int'l. Fed'n. of Pharm. Mfrs. and Ass'ns., *Medical Dictionary for Regulatory Activities Introductory Guide Version 11.0* (2008).

[13] Because the coding system allows for a single patient to be recorded as having experienced several types of tissue damage from a single incident, these data have been "deduped" so that each identified instance of a reaction represents a single patient.

drugs involved reactions MedDRA classifies as related to the ISMP report reactions, for a PRR of 2.9, with a chi-square of 520. Once again, although these numbers do not distinguish IV drip from IV push, at minimum, they create a warning signal that should have triggered further investigation.

Ultimately, however the specific data are interpreted, there is no evidence that Wyeth ever performed these basic and simple tests fundamental to postmarketing surveillance, let alone any of the more sophisticated analyses available to it. In other words, FDA may have generally known that there had been reports of gangrene and tissue necrosis, but there is no evidence that Wyeth even attempted to communicate to FDA (or physicians) the frequency and severity of these risks.[14] Nor was it FDA's responsibility to mine its own data regarding each drug on the market. *See* 21 C.F.R. §314.80(b) (placing responsibility for postmarket surveillance on the manufacturer); CDER Guidance. Though the United States claims that FDA, and not the manufacturer, has the responsibility to "decide when safety information should be included in the labeling for a product," U.S. Br. 23 (quotations omitted), in fact, primary responsibility for the label at all times rests with the manufacturer. *See* 21 C.F.R. §201.80(e) ("The labeling *shall* be revised to include a warning as soon as there is reasonable evidence of an association of a serious hazard with a drug." (emphasis added)) (older drugs); 21 C.F.R. §201.57(c)(6)(i) ("the

[14] FDA itself has stated that "new" information allowing manufacturers to change labeling without prior FDA approval includes information about frequency or severity of known risks, or new analyses of older data. *See* 73 Fed. Reg. 2848, 2850 (2008).

labeling *must* be revised" (emphasis added)) (newer drugs). Thus, there are strong indications that Wyeth failed to meet regulatory obligations, and that FDA failed to consider a significant source of information when examining Phenergan.

D. Supplying Physicians with Accurate Information

As the above discussions show, there has been a stark divergence between the medical profession's understanding of Phenergan's risks, and the actual dangers the drug poses. As a matter of simple communication, the FDA-approved label has been insufficient to inform doctors of the relevant risks. This is why the United States is incorrect to argue that under federal regulations, manufacturers are prohibited from strengthening warnings without "new information" suggesting risks of "a different type or greater severity than risks of which FDA had previously been made aware." U.S. Br. 24.[15] There are a variety of reasons why an FDA-approved label might not fully protect patients, including the real possibility that FDA may not anticipate how the drug is *actually used*, or how the labeling is interpreted by clinicians.[16] Manufacturers, not FDA,

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[15] This definition is apparently narrower than the definition of "new" adopted by FDA. *See* 73 Fed. Reg. at 2850.

[16] There is evidence that both industry and FDA are slow to react even when clinicians flatly misunderstand labeling. According to the Institute of Medicine, between 2000 and 2007, several organizations, including the Centers for Disease Control and ISMP, notified FDA that thousands of patients were at risk of injury due to repeated confusion over the similar labeling of

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have the best access to this information, including information about drug marketing and usage, which is why the statutory and regulatory scheme places responsibility on them to monitor adverse events and strengthen safety and dosage information. *See* 21 C.F.R. §§201.57(c)(6)(i), 314.80.[17]

The United States's argument that state courts will undermine FDA's "careful balancing of risks and benefits" is beside the point. U.S. Br. 22. Respondent is not advocating that States determine when a product

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two different drugs. *See* Institute of Medicine of the National Academies, *The Future of Drug Safety: Promoting and Protecting the Health of the Public* 279 (2007) ("Institute of Medicine Report"). "For about a year, the response by industry and the FDA to the error notification was that 'providers should read the label.' ...When the manufacturer sent the FDA a revised label for approval, it remained at the agency for 6 months without action being taken." *Id.*

[17] The United States argues that the approval process would be "undermined" if the regulations were interpreted to allow manufacturers "to make unilateral changes to labeling the day after FDA's approval based on information that was previously available." U.S. Br. 21. This argument ignores the actual context in which these regulations arise – namely, one in which manufacturers routinely resist stronger warnings. FDA had no reason to draft its regulations to protect against an overwarning manufacturer, because such manufacturers do not exist. As this Court stated in *Geier v. American Honda Motor Co., Inc.*, 529 U.S. 861 (2000), "[W]hy should DOT have bothered to impose an airbag ceiling when the practical threat to the mix it desired arose from the likelihood that manufacturers would install, not too many airbags too quickly, but too few or none at all?" *Id.* at 880.

is defective and should be removed from the market despite the benefits it provides to other patients; Respondent seeks only to insure that doctors receive sufficient information to perform their *own* balancing of risks against benefits for their individual patients – a task they are required to perform by the ethics of their profession.[18] There is no reason why such information cannot be presented in a truthful manner that accurately conveys the degree of risk while still leaving the product available to those who need it.[19]

The United States nonetheless argues that, even with full trial protections, a jury, and the likely review of State appellate courts, States will impose "excessive warnings" that will "cause more meaningful risk information to lose its significance" and will "limit physician appreciation of potentially far more significant risks." U.S. Br. 17, 19 (quotations omitted). But this argument "rest[s] solely on the offensive assumption that the public will respond 'irrationally' to the truth."

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[18] FDA's interpretation of the preemptive scope of its labeling regulation would extend not only to claims against the manufacturer, but also to claims against the *doctor* for failing to warn of risks not identified in the labeling. *See* 71 Fed. Reg. 3922, 3836 (2006). In other words, FDA claims it is empowered not only to regulate *products*, but also to regulate the *medical profession* and standards of practice.

[19] The United States also fails to consider that the risks and benefits of a drug may change due to the introduction of newer, safer alternatives. Even if, for example, IV push administration of an anti-nausea drug is necessary for some patients, it may be that after the introduction of safer alternatives, the risks of Phenergan become unacceptably high.

44 Liquormart v. R.I., 517 U.S. 484, 503 (1996). This Court has repeatedly

> reject[ed] the notion that the Government has an interest in preventing the dissemination of truthful commercial information in order to prevent members of the public from making bad decisions. . . . [The] alternative is to assume that this information is not in itself harmful, that people will perceive their own best interests if only they are well enough informed, and that the best means to that end is to open the channels of communication rather than to close them.

Thompson v. W. States Med. Ctr., 535 U.S. 357, 374 (2002).

FDA, as well, has said that physicians should be supplied with all available information so that doctors may make their own informed judgments about the product. For example, since the labeling format revisions, FDA has required that drug labels warn for hazards associated with *other* drugs in the same class, even when the hazard has not been associated with the subject drug. *E.g.*, 21 C.F.R. §201.57(c)(7)(i). In 1979, FDA rejected one commenter's concern that these requirements, as well as the warning requirements generally, would "mislead" physicians, stating:

> The Commissioner does not agree that physicians will be misled by clear and concise statements in prescription drug labeling regarding serious hazards associated with the use of a drug or a listing of adverse reactions

> that occur with the drug or drugs of the same chemical or pharmacological class. The Commissioner believes that practicing physicians will welcome such information so that they can make their best informed medical judgments in the care of their patients.

44 Fed. Reg. 37,434, 37,447 (1979). In other words, FDA recognized that physicians are capable of understanding and assimilating factual, truthful information about a drug's theoretical risks, even when such risks have never materialized.

Nor is there evidence that "the threat of significant damage awards or penalties" will pressure manufacturers to "propose 'defensive labeling,'" as FDA seems to fear. 71 Fed. Reg. at 3935. After FDA noticed a proposal to alter the standards for a manufacturer to strengthen safety information on drug labeling, 73 Fed. Reg. 2,848, several members of Congress, including Representative Henry A. Waxman, Senator Christopher J. Dodd, and Senator Patrick J. Leahy, directed FDA to "describe any cases" in which the manufacturer strengthened warnings, contraindications, precautions, or adverse reactions "in a manner that harmed public health." Letter from Hon. Henry Waxman et al. 4 (Jan. 23, 2008). In response, FDA evaluated label changes received since 2004, and was unable to identify a *single instance* in which a manufacturer had unduly strengthened its warnings; instead, it named three instances in which a manufacturer's proposed changes were rejected as *not strong enough*, and one instance where FDA requested additional data supporting the change, after which it was approved. *See* Letter from Stephen Mason, FDA, to Hon. Henry Waxman 3-4 (Mar. 7, 2008).

In fact, FDA has repeatedly said that warnings required by labeling rules do not represent the sum total of all warnings that a manufacturer may issue, or may be required to issue. In connection with the labeling format revisions, FDA went out of its way to stress that "labeling regulations do not prohibit a manufacturer, packer, relabeler, or distributor from warning health care professionals whenever possibly harmful adverse effects associated with the use of the drug are discovered. The addition to labeling and advertising of additional warnings, as well as contraindications, adverse reactions, and precautions regarding the drug, or the issuance of letters directed to health care professionals . . . is not prohibited by these regulations." 44 Fed. Reg. at 37,447. FDA even cited with approval *McEwan v. Ortho Pharmaceutical Corp.*, 528 P.2d 522 (Or. 1974), which held that FDA labeling requirements represent a minimum duty of disclosure, and that States may impose duties beyond mere compliance with FDA regulations. 44 Fed. Reg. at 37,447.

Manufacturers continue to be permitted to send "Dear Doctor" letters, which warn clinicians of hazards associated with particular drugs. There is no rule requiring that such letters only contain information identical to that in the product labeling, nor is there a requirement that they be reviewed by FDA prior to distribution so long as they are submitted to FDA after mailing. The only content restriction is that the letter may not be false, misleading, or unfair. *See* CDER, *Manual of Policies and Procedures: NDAs: "Dear Health Care Professional" Letters* (July 2, 2003), http://www.fda.gov/Cder/mapp/6020.10.pdf. Once again, this practice demonstrates that FDA is not overly concerned with the possibility of "overwarning."

Further, the United States's argument that uncontrolled warnings will "limit physician appreciation of potentially far more significant risks" is belied by the existence of FDA's own website, http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/psn/, which provides a steady stream of new safety warnings, many of which do not appear in product labeling, and have not, apparently, undergone formal agency "balancing" of risks relative to benefits. Among other things, the website contains notifications when FDA is merely *investigating* potential hazards, even if the "information is preliminary" and there is "scientific uncertainty." FDA, *FDA Studying Potential Safety Issues with Several Drugs* (June 2008), http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/psn/transcript.cfm?show=76#2. After a published article found higher mortality for a particular drug, FDA announced that until it completed its own evaluation, physicians should be aware of the information in the study *in addition* to the "risks and benefits" in the labeling. FDA, *Early Communication About an Ongoing Safety Review* (Nov. 14, 2007), http://www.fda.gov/cder/drug/early_comm/cefepime.htm.[20] And in the Food and Drug Administration Amendments Act of 2007, Congress ordered FDA to make publicly available on the internet an extensive amount of information about the risk profile of each drug, including summaries of certain adverse event data, with no requirement that such information first be approved for

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[20] *See also* FDA, *Early Communication About an Ongoing Safety Review* (Feb. 2008), http://www.fda.gov/cder/drug/early_comm/botulinium_toxins.htm ("FDA is considering, but has not reached a conclusion about whether this information warrants any regulatory action.").

inclusion in labeling. *See* Pub. L. 110-85, §915. In actuality, then, both Congress and FDA have consistently sought to give health care practitioners access to as much accurate information as possible regarding potential hazards, without fear that such information will impede physician appreciation of "more significant risks."

II. COSTS ASSOCIATED WITH DANGEROUS DRUGS

By one estimate, 30% of hospitalized patients experience an adverse drug event. *See* Sandra Kane-Gill et al., *Adverse-Drug-Event Rates for High-Cost and High-Use Drugs in the Intensive Care Unit*, 63 Am. J. Health-Sys. Pharmacy 1876 (2006). Anywhere from 85% to 90% of adverse drug reactions experienced by hospitalized patients are caused by drugs that are "properly" administered, i.e., appropriately prescribed at the correct dosage. *See* Bonnie L. Senst et al., *A Practical Approach to Determining Costs and Frequency of Adverse Drug Events in a Health Care Network*, 58 Am. J. Health-Sys. Pharmacy 1126 (2001); A. Elixhauser and P. Owens, *Adverse Drug Events in U.S. Hospitals*, HCUP Statistical Brief #29 (Apr. 2007), http://www.hcup-us.ahrq.gov/reports/statbriefs/sb29.pdf. Adverse drug reactions increase the length of hospital stays by approximately 2 days, with additional costs to the patient of $1,900 to $7,000. *See* Kane-Gill, *supra*, at 1877; Senst, *supra* at 1127. One study of four hospitals run by the University of New Mexico found that among adverse reactions occurring in hospitalized

patients, 19% were life-threatening, 45% were serious, and 36% were significant. *See* Senst, *supra*, at 1130. Another study found that the costs of drug-related problems among outpatients exceeded $177.4 billion, more than twice the estimate of $76.6 billion in 1995, and more than the costs of medications themselves. *See* F.R. Ernst & A.J. Grizzle, *Drug-Related Morbidity and Mortality: Updating the Cost-of-Illness Model* 41 J. Am. Pharmaceutical Ass'n 192 (2001). And from 1998 through 2005, serious adverse drug events reported to FDA increased 260%, a rate four times faster than the number of outpatient prescriptions written during this period. *See* Thomas J. Moore et al., *Serious Adverse Drug Events Reported to the Food and Drug Administration*, 1998-2005, 167 Archives Internal Med. 1752 (2007). Seventeen percent resulted in fatalities. *See id.* at 1754.

A substantial portion of the costs of these injuries are ultimately borne by third-party payors, such as Medicare and Medicaid, insurance companies, union-based health and welfare funds, and employer sponsored health benefit plans. Adverse drug reactions thus have the potential to have a tremendous impact on the costs of healthcare. However, when an adverse drug reaction can be shown to have been caused, in whole or in part, by the manufacturer's failure to warn of foreseeable risks, third party payors' reimbursement and subrogation rights can serve as a critical mechanism for cost-containment, holding down both healthcare costs and premium expenses. Though precise figures are unavailable, it can be estimated that third-party payors

recover well in excess of $1 billion annually through reimbursement and subrogation.[21]

On average, 1.5 drugs per year were withdrawn from the market over safety concerns between 1993 and 2006, a figure that does not include drugs that increased their warnings or limited their indications. *See* Issa, *supra*, at 179. It is impossible to know the total costs associated with unsafe medications, but there is anecdotal evidence that they are substantial. For example, in January 2006, the New England Journal of Medicine reported that Trasylol, a drug to reduce bleeding during cardiac surgery, drastically increased the risk of kidney failure, heart attacks, and strokes for certain patients. *See* Dennis Mangano et al., *The Risk of Aprotinin in Cardiac Surgery*, 354 New Eng. J. Med. 353 (2006). The article estimated that dialysis costs attributable to Trasylol – on the market since 1993 with an expanded indication in 1998 – were $1 billion a year, and that had patients been prescribed cheaper, safer generics, $250 million annually would have been saved. *See id.* FDA took months to react, questioned the researcher's methodologies, and voted to keep Trasylol on the market

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[21] During fiscal year 2003, Trover Solutions, Inc., a claims-recovery service, reported recoveries of $239.5 million for 40 million lives insured. *See* Trover Solutions, Inc., 2003 Form 10-K, at 29. Today, 250 million Americans have health insurance, and health care costs rose 18% per capita between 2003 and 2006. *See* Carmen DeNavas-Walt, et al., U.S. Census Bureau, *Income, Poverty, and Health Insurance Coverage in the United States: 2006* (Aug. 2007), http://www.census.gov/prod/2007pubs/p60-233.pdf; Kaiser Family Foundation, *National Health Expenditures Per Capita, 1995-2006* (May 2008), http://facts.kff.org/chart.aspx?ch=203.

even after learning that Bayer, the manufacturer, had failed to disclose a study of 67,000 patients that confirmed Dr. Mangano's results. *See* Kris Hundley, *Drug Warnings Fall Flat*, St. Petersburg Times, Aug. 5, 2007, at 1A. Trasylol was ultimately withdrawn in November 2007 when a Canadian study was halted after preliminary results showed Trasylol increasing the risk of death. *See* Mike Stobbe, *2 More Studies Link Drug to Deaths*, Deseret Morning News, Feb. 21, 2008, at A6.

Vioxx, approved in 1999 and prescribed to 80 million people before it was recalled in 2004, provides another example. *See* Eric J. Topol, *Failing the Public Health — Rofecoxib, Merck, and the FDA*, 351 New Eng. J. Med. 1707 (2004). By one estimate, Vioxx caused between 88,000 and 139,000 sudden heart attacks or deaths. *See FDA, Merck and Vioxx: Putting Patient Safety First? Hearing Before the S. Comm. on Finance*, 108th Cong. 14 (2004) (statement of Dr. David J. Graham). In April 2008, the Journal of the American Medical Association reported that Merck had waged an intentional campaign to distort the results of its clinical trials and to present company research as independent in order to conceal Vioxx's risks from FDA. *See* David Brown, *Maker of Vioxx is Accused of Deception*, Wash. Post, Apr. 16, 2008, at A1. In 2007, Merck agreed to settle lawsuits filed by patients and their family members for $4.85 billion. *See id.*

Petitioner's amici argue that, in most instances, patients and their insurers, rather than drug manufacturers, should be forced to bear the costs of injuries associated with drugs found to carry insufficient

warnings. *E.g.*, Brief of John E. Calfee et al. 16. But manufacturers are far better positioned to bear the costs of injuries caused by their products. Manufacturers, with their superior risk information, are best able to take precautions. Further, in 2006, the pharmaceuticals industry was the second most profitable in the country, second only to mining/crude oil production, and was more than three times as profitable as the median for all Fortune 500 companies. *See* Kaiser Family Foundation, *Profitability of Pharmaceutical Manufacturers Compared to Other Industries*, 1995-2006 (Jan. 2008), http://facts.kff.org/chart.aspx?ch=218. Meanwhile, national health expenditures per capita rose nearly 47% from 2000 to 2006. *See* National Health Expenditures, *supra*.

Petitioner's amici contend that drug manufacturers hesitate to introduce new, beneficial medications for fear of crushing liabilities. *E.g.*, Calfee Br. 16. But there is scant evidence of pharmaceutical companies' hesitancy. Even though drug manufacturers have always been exposed to State tort liability, *see Riegel v. Medtronic, Inc.*, 128 S.Ct. 999, 1019 (2008) (Ginsburg, J., dissenting), they continue to take risks both in their development of new drugs and their marketing of them. For example, direct to consumer advertising increased 330% between 1996 and 2005, despite the widespread view that aggressive marketing of newer drugs, before there is sufficient data about their safety profile to enable patients and doctors to make informed decisions about them, can result in unnecessary injuries to patients. *E.g.*, Julie M. Donahue, *A Decade of Direct-to-Consumer Advertising of Prescription Drugs*, 357 New Eng. J. Med. 673, 674, 678-79 (2007); R.L. Kravitz

& R.A. Bell, *Direct-to-Consumer Advertising of Prescription Drugs: Balancing Benefits and Risks, and a Way Forward*, 82 Clinical Pharmacology & Therapeutics 360, 361 (2007). Despite these risks, and the associated risks of liability, most direct to consumer advertising begins within a year of the drug's introduction. *See* Donahue, *supra*, at 678-79. In fact, according to the Institute of Medicine, pharmaceutical labeling today poses risks to patient health not because of "overwarning" or "defensive warning," but because, among other things, labels may contain "extraneous, unnecessary commercial information" and "[o]veremphasis on company logos and trade dress." Institute of Medicine Report, *supra*, at 276-77.

In short, whatever inhibitions pharmaceutical companies may feel about bringing new drugs to market in the face of uncertain liabilities, they are apparently far outweighed by manufacturers' desire to create markets for their products. For this reason, there is no reason to upset the balance between federal and State regulation of pharmaceuticals that has existed virtually unchanged since 1962.

CONCLUSION

Phenergan presents an example of how insufficient manufacturer vigilance, coupled with lax regulatory oversight, can leave doctors critically uninformed of serious risks to their patients. It is precisely because tragic situations like these are all too common that, for decades, courts have recognized that both States and FDA have important roles to play in overseeing drug safety. If States are stripped of that role, patients' health will be put in jeopardy, with corresponding increases in the cost of medical care. The decision of the Vermont Supreme Court should be affirmed.

Respectfully submitted,

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WYETH,

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DIANA LEVINE,

Respondent.

On Writ of Certiorari to the Supreme Court of Vermont

BRIEF OF JOHN E. CALFEE, ERNST R. BERNDT, ROBERT HAHN, TOMAS PHILIPSON, PAUL H. RUBIN, AND W. KIP VISCUSI AS *AMICI CURIAE* SUPPORTING PETITIONER

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INTEREST OF *AMICI CURIAE*[1]

Amici are economists and economics professors who teach and write on the economic impacts of regulation, including pharmaceutical regulation, and on health care policy, and who wish to ensure that

[1] The parties have consented to the filing of this *amicus* brief. Pursuant to Rule 37.6, *amici* state that this brief was not authored in whole or in part by counsel for any party, and that no person or entity other than *amici* or their counsel made a monetary contribution to the preparation or submission of this brief.

the Court fully considers the adverse effects that might arise from the Vermont Supreme Court's decision in *Wyeth v. Levine*, if that decision is upheld by the U.S. Supreme Court. *Amici* have no stake in the outcome of this case. They are filing this brief solely as individuals and not on behalf of the institutions with which they are affiliated.

John E. Calfee is a Resident Scholar at the American Enterprise Institute. He has written extensively on Food & Drug Administration (FDA) policy, health care policy, and the pharmaceutical and drug markets. Dr. Calfee is the author of many publications on pharmaceutical and health care issues. *See, e.g.*, John E. Calfee, *Price, Markets, and the Pharmaceutical Revolution* (2000) and Claude Barfield and John E. Calfee *Biotechnology and the Patent System: Balancing Innovation and Property Rights* (2007). Dr. Calfee previously was a visiting fellow at the Brookings Institution and an associate professor at the Boston University School of Management.

Ernst R. Berndt is the Louis B. Seley Professor of Applied Economics, Finance and Accounting at the MIT Sloan School of Management, Co-Director of the Biomedical Enterprise Program at Sloan School and the Harvard-MIT Division of Health Sciences and Technology, and Co-Director of the MIT Center for Biomedical Innovation. He has published widely in health economics and pharmaceutical regulation. Among his publications are *Opportunities for Improving the Drug Development Process: Results from a Survey of Industry and the FDA*, National Bureau of Economic Research working paper 11425 (with Adrian H. Gottschalk and Matthew W. Strobeck), and *Cost-benefit analysis of the FDA: The case of the*

prescription drug user fee acts, J. Pub. Econ. v. 92, No. 5-6, pp. 1306-1325 (June 2008) (with Tomas Philipson, Adrian H.B. Gottschalk, and Eric Sun).

Robert Hahn is executive director of the Reg-Markets Center and a senior fellow at the American Enterprise Institute. His research focuses on the costs and benefits of regulation. *See, e.g.*, Robert Hahn and Paul C. Tetlock, *Has Economic Analysis Improved Regulatory Decisions?*, J. Econ. Perspectives, Vol. 22, no. 1, pp. 67-84 (Winter 2008).

Tomas Philipson is a Professor at The Irving B. Harris Graduate School of Public Policy Studies and an associate member of the Department of Economics. He has been a visiting faculty member at Yale University, a visiting fellow at the World Bank, a Senior Economic Advisor to the head of the Food and Drug Administration (FDA), and Senior Economic Advisor to the head of the Centers for Medicare and Medicaid Services. Philipson has published widely on health economics and FDA regulation and twice received the Kenneth Arrow Award of the International Health Economics Association. *See, e.g., Cost-benefit Analysis of the FDA: The case of the prescription drug user fee acts*, J. Pub. Econ. v. 92, No. 5-6, pp. 1306-1325 (June 2008) (with Ernst R. Berndt, Adrian H.B. Gottschalk, and Eric Sun); and *Is the Food and Drug Administration Safe and Effective?*, J. Econ. Perspectives, vol. 22, no. 1, pp. 85-102 (Winter 2008) (with Eric Sun).

Paul H. Rubin is Samuel Candler Dobbs Professor of Economics and Law at Emory University and Editor in Chief of *Managerial and Decision Economics*. He has held several senior government positions, including Chief Economist at the U.S. Consumer Product Safety Commission and Assistant

Director in the Bureau of Economics at the Federal Trade Commission. He has published many articles on drug regulation and tort law and their effects. *See, e.g., Matching Prescription Drugs and Consumers: The Benefits of Direct Advertising*, 313 New Eng. J. Med. 513-515 (Aug. 22, 1985) (with Alison Masson).

W. Kip Viscusi is the University Distinguished Professor of Law, Economics, and Management at Vanderbilt University. He was previously a professor at Harvard Law School and the Duke University and Northwestern University departments of economics. He has written extensively on products liability, hazard warnings, and risk regulation generally. Among his publications are *Reforming Products Liability* (Cambridge: Harvard University Press, 1991); *Deterring Inefficient Pharmaceutical Litigation: An Economic Rationale for the FDA Regulatory Compliance Defense*, Seton Hall L. J., vol. 24, no. 3, pp. 1437-1480 (1994) (with Steven Rowland, Howard Dorfman, and Charles Walsh); and *Economics of Regulation and Antitrust*, 4th ed. (Cambridge; MIT Press, 2005) (with Joseph Harrington and John Vernon).

SUMMARY OF ARGUMENT

Prominent in arguments opposing preemption of state tort law liability for alleged inadequacies in prescription drug labeling is the argument that such liability can complement FDA regulation by improving on a regulatory scheme that fails to provide adequate deterrence against the marketing of unsafe or inadequately labeled drugs. The premise of this argument is faulty. Fundamental principles of economics and numerous studies of FDA drug regu-

lation reveal that FDA in fact errs on the side of overregulation of prescription drugs. Product liability litigation focused solely on one side of the prescription drug public health equation leads to further distortions of the drug approval and labeling process and exacerbates FDA's inherent overly cautious approach. Preemption of state tort law where it conflicts with FDA requirements will minimize these distortions and thereby maximize public health.

FDA's incentive to overregulate is clear upon examination of the underlying forces that can skew its regulatory decisionmaking. In particular, FDA faces substantial criticism when it mistakenly approves drugs that should not have been approved ("Type I errors"), but considerably less criticism when it fails to approve drugs that should have been approved ("Type II errors"). As a result, FDA has an incentive to be overly cautious in approving new drugs, even though the failure to approve a beneficial drug can lead to more significant public health harms than mistaken approval of potentially dangerous drugs. The same FDA tendency toward over-caution (Type II errors) carries over to regulation of the drug label, where FDA has an incentive toward over-warning and undue contraindications. Such excessive warning language also has adverse public health consequences.

State tort lawsuits exacerbate the problems of FDA's overly cautious approach by imposing additional requirements on pharmaceutical companies to add new warnings or contraindications. These requirements lead to a host of distortions in drug marketing and availability that have adverse consequences for public health and wellbeing. Preemption provides an important safeguard against

expected FDA Type II errors by countering the exacerbating impact of state tort lawsuits for failure to warn.

ARGUMENT

I. STATE TORT LAWSUITS EXACERBATE PROBLEMS CAUSED BY FOOD & DRUG ADMINISTRATION OVERREGULATION AND OVERWARNING

A. Incentives Facing FDA Regulators Result in Excess Caution in Drug Approval.

In approving the safety and efficacy, of prescription drugs, FDA faces the possibility of two types of error. First, it can approve a drug that should not have been approved because of safety problems. These errors are called Type I errors. Second, it can fail to approve a drug that should have been approved. These errors are called Type II errors. Under well-established economic principles, the question whether FDA is more likely to commit Type I errors or Type II errors can be answered by focusing on the societal or institutional incentives that push FDA to err on one side or the other.[2] Repeated economic investigation of this question indicates that FDA incentives are skewed toward excessive caution in the regulation of drug development and the approval of new drugs, *i.e.*, Type II errors.[3]

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[2] *See* Henry I. Miller, *First, Do No Harm*, Hoover Digest, No. 4 (2000), *available at* http://www.hoover.org/publications/digest/3493341.html.

[3] *See, e.g.*, Sam Peltzman, *Regulation of Pharmaceutical Innovation: The 1962 Amendments* (1974) ("These measurable effects [of missed benefits from slower new drug approvals, gains from reduced waste on ineffective drugs, and reduced

This skewing can be best understood by considering the likely consequences to FDA's image of a Type I versus a Type II error. When deciding whether the benefits of a proposed new drug exceed its risks, FDA staff know that if they commit a Type I error—the approval of a drug that turns out to be insufficiently safe once marketing begins—their error will become known. Because the harmful side-effects of the drug may be highly visible, a Type I error can and often does lead to impassioned criticism of the agency. On the other hand, a Type II error—the failure to permit marketing of a drug that would in fact provide benefits in excess of harms—is typically

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benefits from competition] add up to a net loss of $250 to $350 million, or about 6 percent of total sales"); Sam Peltzman, *An Evaluation of Consumer Protection Legislation: The 1962 Drug Amendments*, 81 J. Pol. Econ. 1049 (1973), *reprinted in Chicago Studies in Political Economy* 303-48 (George J. Stigler ed., University of Chicago Press 1988) (to same effect); William M. Wardell & Louis Lasagna, *Regulation and Drug Development* 97 (1975) ("In examining the balance sheet for individual therapeutic categories (Chapter VII), it was shown that, in many therapeutic areas, useful and even uniquely effective or safe drugs have been introduced in Britain substantially earlier than in the United States, and at any given time the United States lacks a number of such drugs."); Kenneth Kaitin & Jeffrey Brown, *A Drug Lag Update*, 29/2 Drug Info. J. 361, 372 (1995) ("Despite numerous regulatory reform efforts in this country directed toward accelerating drug development and review processes (described in detail in another section of this White Paper), the United States continues to lag behind other countries in the availability of important new therapeutic products."); Henry I. Miller, *To America's Health: A Proposal to Reform the Food and Drug Administration* 43 (2000) ("Type 2 errors in the form of unreasonable governmental requirements and decisions can delay the marketing of a new product, lessen competition to produce it, and inflate its ultimate price. They can even prevent marketing of a product entirely.").

known only by the relatively few persons who are intimately involved in developing the drug and are largely hidden from patients and the larger medical community who suffer the consequences of the error. Yet the adverse public health impact of a failure to approve a beneficial drug may be even more severe than the approval of an insufficiently safe drug.

Moreover, Type I errors in approving unreasonably unsafe drugs are often quickly corrected precisely because the public learns of the error. But the failure to approve a beneficial drug may go uncorrected for years, if at all. As a result, the net effect of the asymmetry in public knowledge and publicity is to bias even the best-intentioned FDA regulators towards excessive caution and delay in approving new drugs.

Recent debate over FDA's handling of drug safety, notably in connection with selective serotonin reuptake inhibitor (SSRI) antidepressants and Vioxx, an arthritis pain reliever, and culminating in a recent report from the Institute of Medicine, has made clear that the institutional incentives to avoid Type I errors at the expense of committing more Type II errors are very strong. Criticism of FDA staff in connection with the safety of recently approved drugs vastly exceeds any criticism of agency sluggishness in approving the hundreds of drugs in development in recent years. John E. Calfee, *The Vioxx Fallout, AEI Health Policy Outlook*, Sept.-Oct. 2005; Institute of Medicine, *The Future of Drug Safety: Promoting and Protecting the Health of the Public* (2006); John E. Calfee, *Playing Catch-up: The FDA, Science, and Drug Regulation, AEI Health Policy Outlook*, March 2006; Peter H. Schuck, *FDA Preemption of State Tort Law in Drug Regulation: Finding the Sweet*

Spot, Roger Williams U. L. Rev. (forthcoming 2008), *available at* http://ssrn.com/abstract=1078013 at 14-15.

Notably, however, there is no evidence that FDA's overly cautious approach has resulted in the approval of fewer unsafe drugs. To the contrary, numerous studies have concluded that FDA's many years of administrative delay in approving new drugs has caused reductions in the benefits to be gained from new drug development while contributing few, if any, tangible reductions in drug-related public health risks. For example, comparisons of drug approval regimes in the United States, Spain and the U.K. demonstrate that the more rapid drug approval timelines in the European countries have not led to an increased rate of subsequent drug safety withdrawals in those countries, as would be expected if FDA's cautious approach prevented the approval of unsafe drugs. Olav M. Bakke, et al., *Drug Safety Discontinuations in the United Kingdom, the United States, and Spain from 1974 through 1993: A Regulatory Perspective*, Clinical Pharmacology and Therapeutics vol. 58, p. 108 (1995) (noting post-approval drug withdrawals of, respectively, 3% in U.S. and Spain and 4% in U.K.). Likewise, various researchers—including the Institute of Medicine—have examined drug safety before and after the enactment in the United States of the Prescription Drug User Fee Act of 1992 and found that the procedures in the Act allowing faster new drug approvals have not resulted in any diminution of drug safety. *See* Institute of Medicine, *The Future of Drug Safety: Promoting and Protecting the Health of the Public* 3: 5-8 (2006) (reviewing the effects of the Prescription Drug User Fee Act of 1992). And a recent econometric study found that the faster drug

approval times secured under the Act have demonstrably improved consumer welfare. *See* Tomas Philipson et al., *Cost-benefit Analysis of the FDA: The case of the prescription drug user fee acts*, J. Pub. Econ. v. 92, No. 5-6, pp. 1306-1325 (June 2008); Tomas Philipson & Eric Sun, *Is the Food and Drug Administration Safe and Effective?*, J. Econ. Perspectives, vol. 22, no. 1, pp. 85-102 (Winter 2008).

B. The Same Perverse Incentives Result in Excess Caution by FDA in Drug Labeling.

When FDA approves a new drug, it also approves a detailed label to accompany the drug. The label contains indications (conditions to be treated), dosage, administration, and other details including warnings and contraindications, along with summaries of clinical trials and other data. These labels are designed for use by learned intermediary physicians (without whom prescription drugs may not be obtained), although others, including patients, may also make use of labels. As new information arrives about the risks and benefits of approved drugs, FDA continues to review the drug labels and effects labeling changes as appropriate. FDA employs specialized experts in the field to conduct this ongoing review and gathers voluminous post-marketing information from pharmaceutical firms, medical care providers, and other sources. *See, e.g.*, *Should FDA Drug and Medical Device Regulation Bar State Liability Claims?: Hearing Before the H. Comm. on Oversight & Gov't Reform* (testimony of Randall Lutter, FDA Deputy Commissioner for Policy) (May 14, 2008) ("Lutter Testimony").

FDA has long recognized that labels must give varying degrees of emphasis to specific items of information, and that labels should not contain all information of possible interest. *See* Final Rule, Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products, 71 Fed. Reg. 3922, 3968 (Jan. 24, 2006). FDA has for many years sought to modify and improve drug labels while avoiding the constant danger of overwarning. *Id.*; Lutter Testimony. If all potentially negative information were to be included, such as every known possible side-effect, two adverse consequences would follow. One is overwarning: the presence on labels of unfounded or disproportionately prominent warning information, which could deter or discourage drug use that would be beneficial after taking reasonable account of risks and benefits. The second is "clutter": the presence of so much information that physicians would find it hard to distinguish important information from relatively unimportant information and might not even bother to peruse all the information. 71 Fed. Reg. at 3935, 3968.

FDA's decisions about drug labels are strongly affected by the incentives faced by FDA staff. We have described how those incentives cause FDA to exercise excessive caution when approving new drugs. Similar reasoning applies to FDA decision-making about what risk and benefit information to require in drug labels. *See* W. Kip Viscusi, et al., *Deterring Inefficient Pharmaceutical Litigation: An Economic Rationale for the FDA Regulatory Compliance Defense*, Seton Hall L.J., vol. 24, pp. 1437, 1469 n.118 (1994). When deciding about the contents of new drug labels and changes in labels for approved drugs, FDA is once again faced with the possibility of both Type I and Type II errors, *i.e.*, providing

inadequate warnings or requiring warning language and contraindications that overstate risk and discourage beneficial use. And once again, the incentives facing FDA in making that decision cause FDA to err on the side of being overly cautious. In deciding not to require a specific warning, for example, the FDA staff faces the prospect of vigorous, public criticism if patients are harmed by the drug, even if the more aggressive warning was not scientifically warranted or would have lead to disincentives in drug usage that outweighed any potential reduction in risks. Far less criticism is likely to occur if the label warns too strongly about harms that in fact almost never occur, or if the label contraindicates certain uses that are likely to be more beneficial than harmful for patients. Patients would probably not know that they had foregone treatments that in fact would have been worth the true risks, and the victims of this FDA error accordingly will never call FDA to task. On the whole, the agency is likely to be far more risk averse than is justified by the actual balance of risks and benefits as known at the time.[4]

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[4] For example, the label for Rotateq, the rotavirus vaccine, was recently amended to include a warning against intestinal blockage, a rare but genuine problem with an *earlier* rotavirus vaccine that was removed from the market. FDA took this action even though extremely large clinical trials involving tens of thousands of subjects had revealed no excess likelihood of blockage for Rotateq compared to a placebo. *Label on Merck Vaccine to Disclose a Death*, Wall St. J., May 2, 2008, at B8.

C. State Tort Product Liability Lawsuits Exacerbate the Problems of FDA's Excess Caution.

While advocates of state tort law prescription drug litigation often argue that litigation requirements complement FDA requirements by countering the risk of FDA underwarning or underregulation, the economic analysis of FDA incentives in the drug and drug labeling approval process demonstrates that FDA is far more likely to err in the other direction. Accordingly, rather than creating requirements that cure FDA Type I errors, state tort law creates requirements that exacerbate FDA Type II errors by causing pharmaceutical manufacturers to hold back on seeking approval of new drugs or to add defensive labeling, including further undue contra-indications or overwarnings that further squeeze out physician understanding of more significant labeled information.

In state tort lawsuits, juries necessarily focus on a highly specific personal tragedy rather than on societal trade-offs, giving more weight to the harm allegedly suffered by the plaintiff than to the benefits realized by past and future non-injured users of the drug, because benefited patients will play no role in the trial. Given the one-sided nature of their inquiry, there is little reason to expect the lay jurors' labeling decisions to be superior to those of FDA in terms of balancing the risks and benefits of additional contraindications and warnings on the drug label. *See Riegel v. Medtronic, Inc.*, 128 S. Ct. 999, 1008 (2008). Rather, the jury balance will be skewed in favor of more warnings. Of course, juries will not always decide for the plaintiff. But when they do, there is an excellent chance that the verdict will fault

the manufacturer for failing to provide an over-warning or unwarranted contraindication or warning language that would have unduly cluttered the drug label, given that the label already reflects FDA's excess caution.

The impact of this added layer of tort liability overdeterrence leads to numerous adverse consequences that are contrary to public wellbeing, such as:

1. *Limiting drug availability*: Because prescription drug product liability lawsuits often involve allegations of substantial harm, plaintiff verdicts not uncommonly involve sizable awards for pain and suffering damages, punitive damages, or both. Experience has shown that pharmaceutical firms often treat a large damages verdict as a predictor of more such verdicts to come. *See* Paul H. Rubin, John E. Calfee, and Mark F. Grady *BMW vs Gore: Mitigating the Punitive Economics of Punitive Damages*, Sup. Ct. Econ. Rev., vol. 5, pp. 179-216 (1997). While estimates of the cost of liability for pharmaceuticals are few, liability costs are not trivial. For example, a report prepared by the Council of Economic Advisors found that in 2000, liability costs across all U.S. industries were $180 billion, or roughly 1.8 percent of GDP.[5] In the area of drugs and medical devices, Richard Manning identified liability costs for the diphtheria-pertussis-tetanus vaccine by comparing changes in the price of the diphtheria-tetanus vaccine, estimating that at their peak, expected liability costs accounted for roughly 90

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[5] Council of Economic Advisors, *Who Pays for Tort Liability Claims? An Economic Analysis of the U.S. Tort Liability System* (2002).

percent of the vaccine's price.[6] In related work, Manning found that differences in product liability regimes can explain much of the difference in Canadian and U.S. prices on drugs.[7]

The expected costs of product liability litigation are added to a firm's cost-benefit analysis in the marketing of drug products and can lead to the unavailability of drug products, both because some patients may no longer be able to afford treatment and because the expected litigation costs may drive products off the market entirely. For example, childhood vaccine manufacturers quickly raised prices and in many cases exited the market in the wake of a few adverse verdicts in the 1980s. *See* Richard L. Manning, *Changing Rules in Tort Law and the Market for Childhood Vaccines*, J.L. & Econ., vol. 37, no. 1, pp. 247-286 (1994). The anti-nausea drug Bendectin was withdrawn from the market in 1983 after a small number of adverse verdicts (which were subsequently reversed), despite FDA insistence that the drug did not cause the birth defects that gave rise to litigation. *See* Paul H. Rubin, John E. Calfee, and Mark F. Grady, *BMW vs Gore*: *Mitigating the Punitive Economics of Punitive Damages*, Sup. Ct. Econ. Rev. vol. 5, pp. 179, 194 (1997); *see also* American Medical Association, Report of the Board of Trustees, *Impact Of Product Liability On The Development Of New Medical Technologies* 1, 79 (1988) ("AMA Board Report") ("Certain older technologies have been removed from the market, not because of sound scientific evidence indicating lack of safety or efficacy

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[6] Richard M. Manning, *Changing Rules in Tort Law and the Market for Childhood Vaccines*, vol. 37, no. 1, J.L. & Econ. 247-75 (1994).

[7] *Id.*

but because product liability suits have exposed manufacturers to unacceptable financial risks.").

2. *Disincentives for Research & Development*: The costs imposed by product liability litigation have an impact not only on the availability of drugs already on the market but on the pipeline for new drugs, because pharmaceutical companies necessarily factor these costs into decisions whether to incur the significant expense required to research and develop drug products and bring them to the market. Where the level of risk is high, the risk of state tort law liability is inversely related to investment in research and development activity.[8] Firms invest less in drugs that promise to provide substantial clinical benefits but also have significant side-effects (such as many drugs for cancer and multiple sclerosis). Thus, particularly to the extent companies are faced with state tort liability risks that are largely divorced from the FDA balancing of risks and benefits in drug and drug labeling approval, the financial payoff from researching these drugs and bringing them to market is reduced, causing fewer such drugs to be made available to patients. *See* Louis Lasagna, *The Chilling Effect of Product Liability Development*, in The Liability Maze: The Impact of Liability Law on Safety and Innovation 334, 335-37 (Peter W. Huber & Robert E. Litan eds., 1991); National Research Council & Institute of Medicine, *Developing New Contraceptives* 141 (1990) (unpredictable nature of litigation is a significant disincentive for fertility research and development); AMA Board Report at 79 ("Innovative new products are not being developed or

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[8] Michael J. Moore & W. Kip Viscusi, *Product Liability Entering the Twenty-first Century: The U.S. Perspective* 25, 27 (2001).

are being withheld from the market because of liability concerns.").

3. *Loss of FDA control over drug labeling*: Even a single costly loss in a state tort lawsuit alleging failure to warn imposes a legal standard that effectively requires a manufacturer to make changes in its labeling to avoid anticipated costs of future litigation. Although it theoretically might be possible to change labels only for drugs sold in the state in which the lawsuit was brought (assuming such a state-by-state approach was legal), this seems unlikely. Paul H. Rubin, John E. Calfee, and Mark F. Grady *BMW vs Gore: Mitigating the Punitive Economics of Punitive Damages*, Sup. Ct. Econ. Rev., vol. 5, pp. 179-216 (1997). For drugs used in doctors' offices, a state-by-state labeling arrangement would require considerable control over the actions of wholesalers, who are normally free to resell their supply more or less where they please. It would also be hard to prevent patients from using the drug in another state after purchase. Finally, advertising and marketing, which involve risk communication, would become far more complex. Thus it seems likely that the label would be changed nationwide, not just in the state in which the adverse verdict occurred. As a result, a single state tort judgment could effectively wrest control of nationwide drug labeling requirements from FDA, thus depriving the medical community in all states of the benefits of FDA expert determinations on proper and balanced drug warnings.

4. *Defensive labeling*: Firms that suffer adverse verdicts would reasonably attempt to predict other warnings which, if added to the label, might prevent costly litigation in the future. Their competitors, who can be expected to pay close attention to litigation

and its outcomes, would perform similar analyses on their own drugs. With no way to know exactly what would be required through future litigation, firms are likely to add new warning language and contra-indications and create overly crowded labels that seek to anticipate a wide variety of potential plaintiff allegations. *See* Wesley A. Magat and W. Kip Viscusi, *Informational Approaches to Regulation* 1-17, 87-105 (MIT Press 1992) (discussing research showing that substantial increases in the amount of information included on a label decreases the performance of the hazard warning by causing information overload); *see also* W. Kip Viscusi, *Reforming Products Liability* 151 (1991); Aaron D. Twerski et al., *The Use and Abuse of Warnings in Products Liability – Design Defect Litigation Comes of* Age, 61 Cornell L. Rev. 495, 514 (1976). Much of this new warning information would have greater prominence than would be justified by the balance of risks and benefits (precisely because FDA declined to require such information notwithstanding its tendency toward excessive caution). The effect would be to discourage beneficial use of drugs whose labels contain these litigation-induced contraindications and warnings.

As the FDA and others have long recognized, faced with state tort liability regardless of FDA approval of specific warning language, manufacturers may seek to supply warnings about virtually all possible harms that might form the basis for a lawsuit. 71 Fed. Reg. at 3935. For example, a series of Wall Street Journal articles published in 2005 noted that the three erectile dysfunction drugs on the market each carried labels more than 20 pages long. Scott Hensley, *Long Labels Help Drug Firms, But Can Obscure What Matter*, Wall St. J., June 28, 2005; Scott Hensley,

Liability Worries Cloud Drug Labels: In Bloated Package Inserts; Fine Print Can Overshadow Facts of Most Use to Doctors, Wall St. J., July 5, 2005. This litigation-defensive manufacturer tendency to clutter labels with risk information exacerbates FDA's tendency toward excess caution in drug labeling.

5. *Problems exacerbated further in state tort cases alleging missing contraindications*: The concerns discussed above based upon state tort law requirements for added warnings take on particular prominence where, as in this case, a plaintiff is arguing that a drug should have contained a contraindication not required by FDA. Normally, the risk-benefit balancing process for prescription drugs operates at two points: first, when FDA decides what warnings to include on the label and how those warnings are organized, and second, when physicians take account of label warnings as they decide what drugs to prescribe. If failure-to-warn lawsuits cause unfounded or excessive warnings to be placed on the label, physicians can still exercise their usual role in balancing risks and benefits, albeit with less accurate information than would otherwise be available. Contraindications work differently. Physicians are likely to view contraindications as outright bans, because to prescribe in the face of a labeled contraindication is to court a malpractice lawsuit and punitive damages if anything goes wrong. Contraindications therefore largely replace, rather than supplement, the usual balancing of risks and benefits.

Again, there is no reason to expect juries in tort liability trials to perform a better balancing act than FDA. Juries will tend to impose new contraindications, which would prevent physicians from

taking due account of comparative risks and benefits in the highly fact-specific situations in which physicians often making prescribing decisions. As the dynamics of litigation play out, the problem will probably become worse. A contraindication imposed by a jury in one state will likely be translated by pharmaceutical firms into a nationwide contraindication because of the practical inability to limit litigation exposure by single-state label changes. If juries in certain states or regions are especially inclined to find fault with drug labels and impose contraindications, physicians in other states will likely face the same contraindications as label changes are implemented nationwide. Then patients who would have benefited from the contraindicated use will be denied those benefits even if the expected benefit greatly exceeds the likelihood of harm. In extreme cases, manufacturers may choose to remove useful drugs from the market, as happened with many childhood vaccines in the 1980s.

CONCLUSION

The question whether state tort litigation can complement public safety by imposing requirements in excess of those imposed by FDA necessarily depends in part on whether FDA regulation itself is insufficiently or overly cautious. Because FDA is faced with incentives that lead it to stake out overly cautious positions on drug approval and drug labeling, state tort litigation imposing additional requirements leads to a further departure away from the most socially beneficial outcome.

Given this background, it is clear that the public health would only be improved if state tort lawsuits like the one below were held preempted. For the

reasons set forth above, the economist *Amici*, Messrs. Calfee, Berndt, Hahn, Philipson, Rubin, and Viscusi, respectfully submit that the decision of the Supreme Court of Vermont should be reversed.

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Petitioner,
v.
DIANA LEVINE,
Respondent.

On Writ of Certiorari to the Vermont Supreme Court

BRIEF OF THE CALIFORNIA MEDICAL ASSOCIATION AS *AMICUS CURIAE* IN SUPPORT OF RESPONDENT

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INTEREST OF *AMICUS CURIAE*[1]

The California Medical Association ["CMA"] is a nonprofit, incorporated professional association of more than 35,000 physicians who are engaged in the private practice of medicine, in all specialties and modes of practice, in the State of California. Its mission is to promote the science and art of medicine, the care and well-being of patients, the protection of the public health, and the betterment of the medical profession.

CMA and the thousands of physicians and patients it represents have as their highest priority insuring that patients receive the best medical care possible. For that reason, CMA and its members diligently monitor and carefully consider the consequences to patients of important public policy issues such as preemption of pharmaceutical failure-to-warn claims.

Because preemption of pharmaceutical failure-to-warn claims would obstruct physicians' access to complete and truthful information about prescription drug safety and efficacy and force doctors to try to uncover such information on their own, it would compromise patient safety. Preemption would then

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[1] Each party has consented to the filing of this brief. The parties' letters of consent are filed with the Court. No counsel for a party authored in whole or in part, and no party or their counsel made a monetary contribution intended to fund the preparation or submission of this brief.

leave these patients without recourse for drug-related injuries and put physicians at risk by potentially allowing drug manufacturers to shift liability for such injuries to doctors. The unfounded fear of "overwarning,"[2] cannot justify placing patients and doctors at risk.

To protect patient safety, *Amicus,* the California Medical Association, files this brief in support of Respondent Diana Levine on its own behalf and on behalf of its members' patients who will be directly and adversely affected by preemption.

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[2] As used by Petitioner and its *amici*, "overwarning" is loosely defined as including allegedly trivial and scientifically-unjustified information in prescription drug labels. *See, e.g.*, Brief of Pharmaceutical Research and Manufacturers of America and Biotechnology Industry Organization as *Amici* Curiae Supporting Petitioner (Wyeth) [hereafter "PhRMA/BIO Brief"], at 15.

SUMMARY OF ARGUMENT

Physicians serve their patients best when they have access to complete and truthful information about the risks and benefits of the drugs they prescribe. Without it, they cannot properly evaluate the complex interaction between a prescription drug and a patient's unique body chemistry.

Because preempting failure-to-warn claims would make the U.S. Food and Drug Administration ["FDA"] approval the final word on a drug's safety, it would significantly weaken manufacturers' incentives to conduct new safety studies, to monitor their drugs in the marketplace, to improve them post-approval, and to supply FDA and doctors with new or revised safety information. Moreover, it would deprive physicians of the important drug safety information that has unfortunately come to light only in failure-to-warn litigation. In the absence of viable alternative sources for this information, physicians would be unable to provide patients with the best possible care and patient safety would be at risk.

Preempting failure-to-warn claims would also put doctors at risk. First, it may subject them to new and unwarranted liability for the consequences of drug defects and potentially shift financial responsibility for injuries to physicians and patients. In doing so, it may rob physicians of their ability to challenge the adequacy of drug warnings in defense of such claims. This potential for new liability would undermine long-standing efforts to protect doctors from suit and could well drive some physicians from the profession.

Moreover, preemption of failure-to-warn claims may also require that physicians become one-man FDA's as they attempt to uncover hidden or unclear safety risks to protect their patients. This search would add unduly to the considerable time and financial pressures practicing physicians already face.

These demonstrable harms vastly outweigh the absence of any actual risk of alleged "overwarning." Neither Petitioner nor its *amici* has provided this Court with a single instance in which tort litigation has actually forced a word or phrase to be included in any prescription drug label. Instead, they describe public panics, misinformation in the public domain, or so-called "black box" warnings that contain life-threatening, verified risks. Preemption, however, would eliminate none of these things.

Since they have not shown that "overwarning" even exists in this context, Wyeth's *amici* have not demonstrated that alleged "overwarning" has led to underuse of prescription drugs. It is not surprising then that neither Petitioner nor its *amici* have produced a single example of any actual connection between the two, if any exists.

Because preemption is unwarranted and would needlessly put physicians and patients alike at risk, the undersigned *amici* ask that the decision of the Vermont Supreme Court be affirmed.

ARGUMENT

I. By Making FDA Approval the Last Word on a Drug's Safety, Preemption of Failure-to-Warn Claims Would Jeopardize Patient Safety

A. Physicians Require Full and Accurate Information About Drug Safety to Treat Their Patients Safely

The Hippocratic oath mandates that physicians "prescribe regimens for the good of [their] patients according to [their] ability and judgment and never do harm to anyone" or knowingly "prescribe a deadly drug."[3] To satisfy its requirements,

> [Physicians must have access to all relevant medical information regarding . . . various medications that we discuss with and recommend to our patients. Any obstacle placed in the way of full and complete communication with our patients undermines the trust upon which the doctor-patient relationship is

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[3] LEWIS RICHARD FARNELL, THE CULT OF ASKLEPIOS, 269-70 (Oxford: Clarendon Press) (1921).

> based and prevents us from providing the best care we can to our patients.[4]

Treating physicians can provide the best possible care only when they have fullest possible access to the widest available array of truthful information. When examining and treating patients, physicians review the patient's medical history and whatever reliable information is available about a needed drug. FDA acknowledges that it plays only a supporting role in patient care and that "it is essential to the safe use of a drug for the physician to know all adverse reactions that are likely to occur with it."[5] FDA "believes that practicing physicians will welcome such information so that they can make their best informed medical judgments in the care of their patients."[6]

To that end, FDA regulations require that manufacturers include in prescription drug labeling all "[i]nformation that would ***affect decisions about***

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[4] Press Release, Barry B. Perlman, President, New York State Psychiatric Association (June 2, 2004), http://www.oag.state.ny.us/press/2004/jun/jun2b_04_attach2.pdf.

[5] Labeling and Prescription Drug Advertising; Content and Format for Labeling for Human Prescription Drugs, 44 Fed. Reg. 37,434, 37,443 (June 26, 1979).

[6] *Id.* at 37,447.

whether to prescribe a drug,"[7] including "a list of the most frequently occurring adverse reactions."[8] Medical journal boards and FDA have recognized, however, that drug manufacturers sometimes fail to disclose critical safety information about substantial health hazards or misrepresent such facts to doctors. For example, both *The Lancet*[9] and *New England Journal of Medicine* ["NEJM"][10] have harshly criticized Merck for allegedly misleading or failing to disclose to the medical community data regarding cardiovascular risks associated with its arthritis drug Vioxx that both deemed important to patient safety. Similarly, FDA itself is investigating whether Eli Lilly submitted false or misleading data concerning diabetic side effects of its anti-psychotic drug Zyprexa in its promotional materials and sales pitches to doctors.[11]

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[7] 21 C.F.R. § 201.57(a)(10) (2008) (emphasis supplied).

[8] 21 C.F.R. § 201.57(a)(11) (2008).

[9] Richard Horton, Commentary, *Vioxx, the Implosion of Merck, Aftershocks at the FDA*, 364 THE LANCET 1995 (2004).

[10] Gregory D. Curfman et al., Editorial, *Expression of Concern Reaffirmed*, 354 NEW ENG. J. MED. 1193 (2006); Gregory D. Curfman et al., *Expression of Concern: Bombardier et al., Comparison of Upper Gastrointestinal Toxicity of Rofecoxib and Naproxen in Patients with Rheumatoid Arthritis*, 343 NEW ENG. J. MED. 1520 (2000), 353 NEW ENG. J. MED. 2813 (2005).

[11] Alex Berenson, *U.S. Wonders If Zyprexa Drug Data Was Accurate*, N.Y. TIMES, Apr. 25, 2007, at C1; *see also* Thomas O.

FDA lacks the tools and resources to uncover and to provide physicians with this kind of information on its own. The Food Drug and Cosmetic Act ["FDCA"] neither grants FDA subpoena power nor does its limited information-gathering authority extend to documents reflecting internal deliberations over safety hazards or analyses of drug performance.[12] Instead, FDA takes what it gets from drug companies. In fact, "as often as not, the information that agencies do obtain on underlying malfeasance by regulatees comes to them indirectly through tort litigation."[13] These limitations call into question the legitimacy and value to physicians of FDA decisions about prescription drugs. "To the extent that regulatory agencies cannot generate the information they need for accurate

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McGarity, *The Complementary Roles of Common Law Courts and Federal Agencies in Producing and Using Policy-Relevant Scientific Information*, 37 ENVTL. L. 1027, 1051 (Fall 2007); *and* Alex Berenson, *Eli Lilly Said to Play Down Risk of Top Pill*, N.Y. TIMES, Dec. 17, 2006, at A1.

[12] *See* 21 U.S.C. § 355(k) (2008); *and* David C. Vladeck, *Defending Courts: A Brief Rejoinder to Professors Fried and Rosenberg*, 31 SETON HALL L. REV. 631, 633-35 (2001).

[13] THOMAS O. MCGARITY, THE PREEMPTION WAR 204 (Yale Univ. Press 2008) (citing Aaron S. Kesselheim et al., *The Role of Litigation in Defining Drug Risks*, 297 JAMA 308 (2007)).

decision-making, the advantage in technical expertise that they have over the courts is largely lost."[14]

For these reasons, the medical community has recognized that FDA approval does not and cannot assure drug safety nor guarantee that doctors receive the information they need to prescribe drugs safely.[15] The National Academy of Sciences' Institute of Medicine found that deficiencies in FDA's drug safety system directly impacted the quality of risk information provided to physicians.[16] A recent *Journal of the American Medical Association* ["JAMA"] editorial against preemption of failure-to-warn claims explained:

> Curbing frivolous lawsuits is a worthy goal, but limiting legal involvement in the prescription drug arena is likely to

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[14] *Id.* (citing Wendy Wagner, *Stubborn Information Problems and the Regulatory Benefits of Gun Litigation in* SUING THE GUN INDUSTRY 225, 231, 271 (Timothy D. Lytton ed., Univ. of Mich. Press 2005)).

[15] Lawrence O. Gostin, *The Deregulatory Effects of Preempting Tort Litigation: FDA Regulation of Medical Devices*, 299 JAMA 2313, 2314 (2008).

[16] COMM. ON THE ASSESSMENT OF THE U.S. DRUG SAFETY SYS., THE FUTURE OF DRUG SAFETY: PROMOTING AND PROTECTING THE HEALTH OF THE PUBLIC 4 (Alina Baciu et al. eds., Nat'l Acad. Press 2007), *available at* http://www.nap.edu/catalog.php?record_id=11750.

> increase the nation's problem of poorly defined or inadequately presented drug risk information. These case studies indicate that clinical trials and routine regulatory oversight as currently practiced often fail to uncover important adverse effects for widely marketed products. In each instance, the litigation process revealed new data on the incidence of adverse events, enabled reassessments of drug risks through better evaluation of data, and influenced corporate and regulatory behavior. In performing these tasks, lawyers and their clients often find themselves serving as drug safety researchers of last resort.[17]

While *amici* do not necessarily believe that the tort system is the most efficient tool to insure drug safety, "[r]ecent history casts some doubt on the ability of FDA alone to protect the public and, thus, on the wisdom of dispensing with tort law."[18]

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[17] Kesselheim et al., *supra* note 13, at 308-311.

[18] Russell Korobkin, *Who Should Protect the Public? The Supreme Court and Medical Device Regulation*, 357 NEW ENG. J. MED. 1680, 1681 (2007); *see also Bates v. Dow AgroSciences, LLC*, 544 U.S. 431, 451 (2005) (Breyer, J., dissenting) ("tort suits can serve as a catalyst" to aid "in the exposure of new dangers and their consequences").

B. Preemption Would Stop the Flow to Doctors of Critical Drug Safety Information

Preemption of pharmaceutical failure-to-warn claims would obstruct the flow of drug safety information to doctors in several ways. First, it would seriously diminish the drug industry's incentive to disclose safety information to FDA and, through it, to doctors, or to alter its labels to reflect new drug hazards.[19] As one recent commentator explained:

> If courts extended federal preemption to drug claims . . . manufacturers would have little incentive to conduct post-approval clinical studies to examine a drug's safety. The FDA also would lose one of its few bargaining chips in pressuring companies to amend labels to warn of newly discovered risks. If failure-to-warn claims were not actionable, drug companies could effectively resist all efforts by the FDA to expand warnings.[20]

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[19] *Bates*, 544 U.S. at 450.

[20] Jonathan V. O'Steen, *The FDA Defense: Vioxx and the Argument Against Federal Preemption of State Claims for Injuries Resulting From Defective Drugs*, 48 ARIZ. L. REV. 67, 95 (Spring 2006).

In short, preemption would give drug manufacturers "a free pass to avoid making the otherwise statutorily required label changes with no simultaneous, conscious purpose to enhance safety or availability."[21] Drug manufacturers who have, or could, obtain information about increased risk that would otherwise have to be disclosed would be protected from the consequences of their failure to disclose.

This is true even if one believes that FDA has superior expertise in determining drug warnings' contents. Although FDA has historically faced mountains of information about products it regulates, it is not always able to process such information in a timely fashion.

> [T]he FDA can rely on the incentives of the tort system to encourage manufacturers to continue research, reveal research results honestly, monitor scientific literature, and request or issue appropriate warnings. Preemption would remove those incentives, and it is unclear whether the FDA could adequately review drug information under its current

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[21] Mary J. Davis, *The Battle Over Implied Preemption: Products Liability and the FDA*, 48 B.C. L. REV. 1089, 1143 (2007).

staffing and budget without the support of private lawsuits.[22]

As demonstrated above, in addition to diminishing manufacturer incentives, preemption of failure-to-warn claims would also significantly reduce or potentially end doctors' access to drug safety information that comes to light in tort litigation.[23] While physicians do not support unfounded lawsuits, in the absence of alternative sources for such information, they must continue to rely on meritorious lawsuits to reveal significant threats to patient safety.

In recognition of these dangers, major medical journals have strongly opposed preemption because the alleged benefits of providing absolute immunity to drug manufacturers through preemption are far outweighed by the harm to patient care and physicians.[24] It would be a disservice if those most responsible for drug safety enjoyed the protections of preemption while health care

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[22] Howard A. Denemark, *Improving Litigation Against Drug Manufacturers for Failure to Warn Against Possible Side Effects: Keeping Dubious Lawsuits from Driving Good Drugs Off the Market*, 40 CASE W. RES. L. REV. 413, 431 (1990).

[23] Richard A. Nagareda, *FDA Preemption: When Tort Law Meets the Administrative State*, 1 J. TORT L. 1, 45 (2006), *available at* http://www.bepress.com/jtl/vol1/iss1/art4.

[24] *See, e.g.*, Leonard M. Glantz et al., *The FDA, Preemption, and the Supreme Court*, 358 NEW ENG. J. MED. 1883 (2008); Gostin, *supra* note 15, at 2313.

providers and patients were left to suffer the consequences of their drugs' failures and defects alone.

II. Preemption of Failure-To-Warn Claims Would Put Physicians at Risk

A. Preemption May Subject Physicians to New and Unwarranted Liability

It is unlikely that preemption of failure-to-warn claims would immunize doctors from malpractice claims alleging improper drug prescription.[25] While the preamble to 2006 FDA regulations[26] implies that failure-to-warn claims against providers are

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[25] Only a few cases address preemption's impact on malpractice claims and all find that such claims are not preempted. *Nealy v. U.S. Healthcare HMO*, 711 N.E.2d 621, 622 (N.Y. 1999) (ERISA); *Brooks v. Maryland Gen. Hosp., Inc.*, 996 F.2d 708, 714 (4th Cir. 1993) (no preemption of state malpractice law under EMTALA); *Aragon v. Federated Dep't Stores, Inc.*, 750 F.2d 1447 (9th Cir.), *cert. denied*, 474 U.S. 902 (1985) (malpractice claim against attorneys provided by union not preempted); *Evitt v. University Heights Hospital*, 727 F. Supp. 495, 498 (S.D. Ind. 1989) (medical malpractice claim not preempted by COBRA); *see also New York State Conf. of Blue Cross & Blue Shield Plans v. Travelers Ins. Co.*, 514 U.S. 645, 658-68 (1995) (addressing applicability of COBRA to physicians claims); *Hillsborough County v. Automated Med. Labs., Inc.*, 471 U.S. 707, 715 (1985).

[26] *See* Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products, 71 Fed. Reg. 3922, 3933 (Jan. 24, 2006) (effective June 30, 2006) (codified at 21 C.F.R. § 201, 314, 601).

preempted, it does not specifically address malpractice claims. *Id.* In fact, Petitioner argued below that Diana Levine's injuries resulted from her physicians' negligence and did not argue that her claims against her doctors were preempted.[27] Moreover, at a recent hearing on preemption of their claims against manufacturers, Senator Orrin Hatch suggested that the women injured by prescription drugs and medical devices who testified sue their doctors instead.[28]

Most states' laws do not permit FDA approval to render prescription drug warnings adequate as a matter of law.[29] In defending against malpractice claims based upon alleged negligence in prescribing drugs for a patient, doctors may, therefore, question the adequacy of their warnings.

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[27] *See, e.g.*, Brief of Petitioner Wyeth at 19-20; Brief of Respondent Diana Levine at 17-19.

[28] *Short-Change for Consumers and Short-Shrift for Congress?. The Supreme Court's Treatment of Laws That Protect American's Health, Safety, Jobs and Retirement Hearing Before the Senate Judiciary Committee*, 110th Cong. 2nd Sess. (2008) (Statement of Sen. Orrin Hatch), *available at* http://judiciary.senate.gov/hearing.cfm?id=3404.

[29] *See, e.g., Estate of Montagne v. Bristol-Myers Squibb*, 111 P.3d 857 (Wash. App. 2005); *Edwards v. Basel Pharm.*, 933 P.2d 298 (Okla. 1997); *MacDonald v. Ortho Pharm. Corp.*, 475 N.E.2d 65 (Mass.), *cert. denied*, 474 U.S. 920 (1985).

By effectively decreeing that FDA-approved warnings, no matter how opaque, are adequate as a matter of law and charging doctors with knowledge of their contents and meaning, however, preemption may subject doctors to unwarranted medical negligence claims. As the result, physicians would run a significant risk of suit and liability based on the assumption that FDA-approved labels are clear when, in fact, they are not.

Thus, preemption of failure-to-warn claims threatens to shift liability for adverse drug side effects to physicians, undermining decades-long efforts to protect them from tort suits,[30] and to facilitate the drug industry's off-loading financial responsibility for such injuries to doctors and their patients. Such a shift may even force some doctors to abandon their practices.

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[30] *See* Cal. Civ. Code § 3333.2 (West 2007) (limits non-economic damages in suits against health care providers); FLA. STAT. Ch. 768.28 (2008) (recovery limits); FLA. STAT. Ch. 768.73 (2008) (limits punitive damages); TEX. CONST. art. III § 66 (limits non-economic damages in lawsuits against health care providers); TEX. CIV. PRAC. & REM. CODE ANN. § 74.301 (Vernon 2008) (limits non-economic damages); TEX. CIV. PRAC. & REM. CODE ANN. § 41.008 (Vernon 2007) (limits recovery of punitive damages).

B. Preemption Would Place Undue Pressure on Physicians to Uncover Drug Safety Information Independently

It is no secret that physicians face increasing time and financial pressures. In one survey, 75% of the doctors with managed care contracts said they felt pressured to see more patients.[31] Twenty-eight percent "reported that they felt pressure to limit what they told patients about treatment options," 57% felt pressured to restrict their referrals, and nearly a third of these doctors said the pressure was severe enough to compromise the quality of care. *Id.*

Physicians must also deal with an increasing barrage of potentially misleading information about prescription drugs. Physicians perceive that "Internet information often generate[s] patient misinformation, leading to confusion, distress, or an inclination towards detrimental self-diagnosis and/or self-treatment. Physicians felt these influences added a new interpretive role to their clinical responsibilities."[32]

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[31] Kevin Grumbach et al., *Primary Care Physicians' Experience of Financial Incentives in Managed Care Systems*, 339 NEW ENG. J. MED. 1516 (1998).

[32] Farah Ahmad et al., *Are Physicians Ready for Patients With Internet-Based Health Information?*, 8 J. MED. INTERNET RES. e22 (2006), http://www.pubmedcentral.nih.gov/article render.fcgi?artid =2018833.

Industry-generated direct-to-consumer advertising also pressures doctors to explain drug claims and prescribe requested but unwarranted drugs. This Court has acknowledged that pressure.[33] Doctors may also soon be faced with additional scientific studies on unapproved, commonly referred to as "off-label," drug uses if proposed regulations allowing companies to send doctors such information are promulgated.[34] The medical community has recognized, however that, while "[p]eople are viewing reprints as science and they believe that science is objective . . . industry uses research to advance marketing goals."[35]

At the same time, FDA is no longer capable of ensuring that medical professionals receive all relevant information about the risks of prescription medications. In addition to studies previously cited, a 2006 Government Accountability Office report expressed grave concerns about FDA's ability to

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[33] *Thompson v. Western States Medical Center, et al.*, 535 U.S. 357, 378 (2002) (Breyer, J., dissenting).

[34] Draft Guidance for Industry on Good Reprint Practices for the Distribution of Medical Journal Article and Medical or Scientific Reference Publication on Unapproved New Uses of Approved Drugs and Approved or Cleared Medical Devices, 73 Fed. Reg. 9342 (Feb. 20, 2008).

[35] Mike Mitka, *Critics Say FDA's Off-Label Guidance Allows Marketing Disguised as Science*, 299 JAMA 1759 (2008).

monitor the safety of approved drugs.[36] Last year, a subcommittee of FDA's own Science Board "concluded that science at the FDA is in a precarious position: the Agency suffers from serious scientific deficiencies and is not positioned to meet current or emerging regulatory responsibilities."[37] "FDA's inability to keep up with scientific advances," the report explained, "means that American lives are at risk." *Id.* at 3.

Were this Court to preempt failure-to-warn claims, it would reduce significantly the incentive for drug companies to supply doctors and FDA with critical safety information and cut off information generated in pharmaceutical litigation. Without access to such reliable sources of information about a drug's adverse side effects, physicians may have to become "drug safety researchers of last resort"[38] as they attempt to uncover safety information on their own. With little or no help from FDA, none from the courts, with drug companies actively promoting drug benefits

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[36] U.S. GOV'T ACCOUNTABILITY OFFICE, DRUG SAFETY: IMPROVEMENT NEEDED IN FDA'S POSTMARKET DECISION-MAKING AND OVERSIGHT PROCESS 5 (2006), *available at* www.gao.gov/cgi-bin/getrpt?GAO-06-402.

[37] U.S. FOOD & DRUG ADMINISTRATION, REPORT OF THE SUBCOMMITTEE ON SCIENCE AND TECHNOLOGY, FDA SCIENCE AND MISSION AT RISK 2 (2007), *available at* http://www.fda.gov/ohrms/dockets/ac/07/briefing/2007-4329b_02_01_FDA%20Report%20on%20Science%20and%20 Technology.pdf.

[38] Kesselheim et al., *supra* note 13, at 308-311.

but lacking incentive to disclose risks, and with patients increasingly armed with direct-to-consumer advertising and Internet health information, it will become increasingly difficult for physicians to obtain the full and accurate information they must have to treat their patients safely. Consequently, patient safety will suffer and the financial responsibility for that suffering will be disproportionately and unfairly borne by physicians and their patients.

III. Alleged "Overwarning" Does Not Justify Preemption of Failure-to-Warn Claims

Against the backdrop of major drug litigation, it is telling that the drug industry has not provided this Court with a single unwarranted word or phrase ever actually included in any prescription drug label as its result, let alone showed the "proliferation of inappropriate warnings" in FDA-approved labels one *amicus* claims.[39] In the many briefs the industry filed, there is not one example of a failure-to-warn suits' actually causing any manufacturer to include "virtually all known adverse event information, regardless of its importance" in its label.[40] In fact, numerous courts

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[39] *See* PhRMA/BIO Brief at 15. Even FDA's recent discussion of overwarning is entirely theoretical. *See* Requirements on Content and Form of Labeling for Human Prescription Drug and Biological Products, *supra* note 26, at 3935.

[40] *See* PhRMA/BIO Brief at 15.

have rejected the industry's overwarning arguments simply because of the absence of any factual support for them.[41]

The risk to Diana Levine of gangrene or lost limbs from the administration of Phenergan through IV-push injection is hardly insubstantial or speculative. The same is true of FDA-ordered "black-box" suicide warnings now present in the labels of certain anti-depressants.[42] Moreover, where, as here, the issue is not whether a drug should have been used at all but which of several methods of administration should have been employed, the alleged dangers of overwarning – removal of the drug from the market and under-use – are not implicated because the patient would have received the drug either way.

More important, it is impossible to overwarn in the prescription drug context because manufacturers are already obligated by law to include in their labels anything that would affect a physician's decision to prescribe a drug, including recurring adverse events.[43] If information is too trivial or speculative even to

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[41] *See Cartwright v. Pfizer, Inc.*, 369 F. Supp. 2d 876, 886 (E.D. Tex. 2005); *Witczak v. Pfizer, Inc.*, 377 F. Supp. 2d 726, 732 (D. Minn. 2005); *Zikis v. Pfizer*, 2005 WL 3019409 at *4 (N.D. Ill. May 9, 2005); *see also Colacicco v. Apotex, Inc.*, 521 F.3d 253, 277 (3d Cir. 2008) (Ambro, J., dissenting).

[42] *See* PhRMA/BIO Brief at 17.

[43] 21 C.F.R. § 201.57(a)(10), (11) (2008).

change a prescribing decision, its disclosure poses no risk of under-treatment or drug under-utilization sufficient to drive a drug from the market.

There is likewise little actual danger that including allegedly trivial or unsubstantiated information in a drug label would so thoroughly confuse doctors about real dangers that they would be too confused to utilize a drug properly. Justice Breyer noted that "doctors . . . obtain information about individual drugs through many other channels" and are nevertheless able to filter through it.[44] Even with a barrage of Internet health information and direct-to-consumer advertising, physicians have been able to separate reliable information and sources from unreliable ones. Thus, including a little additional information in a prescription drug label is unlikely to flummox completely trained physicians.

Moreover, the drug industry has not expressed any concern about confusing or overwhelming doctors in asserting an alleged constitutional right to send doctors industry-sponsored[45] scientific papers on potential drug benefits, including unapproved off-label

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[44] *Thompson*, 535 U.S. at 378 (Breyer, J., dissenting).

[45] Barton Moffatt et al., *Ghost Marketing: Pharmaceutical Companies and Ghostwritten Journal Articles*, 50 PERSPECTIVES BIOL. MEDICINE 18 (2007).

uses.[46] They have also lobbied FDA for proposed rules to allow immediate dissemination of such materials.[47]

Apparently, overwarning has become an issue for drug companies only as they have tried to promote directly to the public prescription drugs containing warnings written for physicians. In fact, *amici* mistakenly argue that "***patients*** [not doctors] may be deterred from using a needed medicine in the face of intimidating warnings . . ."[48] The alleged examples they discuss do not involve prescription drug labels and, therefore, provide no support for the notion that ***doctors*** have been overwarned.[49] Preemption of failure-to-warn claims will not stop Internet rumors, public panics, or patient non-compliance. Instead, doctors armed with complete and accurate information are the best defense against patient confusion.

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[46] *See, e.g.*, Daniel E. Troy et al, *Pharmaceutical Promotion and First Amendment Rights*, 359 NEW ENG. J. MED. 536, 536-37 (2008).

[47] Draft Guidance for Industry on Good Reprint Practices, *supra* note 34, at 9342.

[48] PhRMA/BIO Brief at 14 (emphasis supplied).

[49] *Id.* at 16-25; Brief of *Amici* Washington Legal Foundation ["WLF"] and American College of Emergency Physicians ["ACEP"] as *Amici* Curiae in Support of Petitioner (Wyeth) [hereafter "WLF/ACEP Brief "], at 16-26.

A. Wyeth's *Amici* Have Not Demonstrated that "Overwarning" in Prescription Drug Labels Exists

Although Wyeth's *amici* attempt to provide examples of overwarning to justify preempting failure-to-warn claims, they fail in that attempt. Several illustrations do not even involve prescription drugs. Only one concerns anything contained in a prescription drug label but addresses risks that FDA itself had already determined were life-threatening and scientifically-warranted. As such, including these risks in a drug's label can hardly be classified as "overwarning." To the extent any of these anecdotes addresses tort lawsuits, it is to blame tort claims on alleged "overwarning" rather than argue, as industry *amici* do, that the lawsuits caused manufacturers to overwarn. Thus, these anecdotes do not demonstrate that alleged overwarning in prescription drug labels as the alleged result of tort claims, if it occurs at all, is so severe as to warrant preempting failure-to-warn claims.

Teen Suicide and SSRI's[50]

Several industry *amici* suggest that the pediatric suicide warnings issued as early as 2003 for certain anti-depressants actually led to an increase in teen suicides in 2003-05 in the U.S. and Europe.[51] The idea that information contained in a so-called "black box" can be considered as "overwarning" has no merit. Only FDA can order a black-box warning.[52] Moreover, black-box warnings are ordered only for what the FDA deems as the most serious, scientifically-justified risks, hardly candidates for the term "overwarning."[53]

Second, these warnings pertain to a mostly unapproved use of these drugs and are, therefore, irrelevant to preemption which makes FDA approval sacrosanct. Despite widespread off-label use, only one

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[50] So-called SSRI's are a class of anti-depressants known as selective serotonin reuptake inhibitors.

[51] Robert D. Gibbons et al., *Early Evidence on the Effects of Regulators' Suicidality Warnings on SSRI Prescriptions and Suicide in Children and Adolescents*, 164 AM. J. PSYCHIATRY 1356, 1361-62 (2007); *see also* WLF/ACEP Brief at 17, PhRMA/BIO Brief at 17-18.

[52] Labeling and Prescription Drug Advertising; Content and Format for Labeling for Human Prescription Drugs, 44 Fed. Reg. 37,434, 37,448 (June 26, 1979).

[53] *See* 21 C.F.R. § 201.57(e)(1) (2008).

of the anti-depressants studied – Prozac – has ever been approved for pediatric use in the United States.[54]

Viewed in their proper light then, pediatric suicide warnings might have provided an illustration of what happens when a medically-verified warning regarding a very serious risk of an off-label use is issued. It is unfortunate that they cannot offer even that modest contribution because the study was limited to "early evidence,"[55] and its conclusions have not been confirmed by more complete and final data.

When statistics for suicide rates for 2005 became available, they revealed that fewer people under 25 committed suicide in 2005 than in 2004 when the black-box suicide warning was ordered.[56] Recent studies conducted in Great Britain confirm that reductions in anti-depressant prescriptions after

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[54] NATIONAL INST. OF MENTAL HEALTH, ANTI DEPRESSANT MEDICATIONS FOR CHILDREN AND ADOLESCENTS: INFORMATION FOR PARENTS AND CAREGIVERS, *available at* http://www.nimh.nih.gov/health/topics/child-and-adolescent-mental-health/anti-depressant-medications-for-children-and-adolescents-information-for-parents-and-caregivers.shtml (last visited Aug. 12, 2008).

[55] Gibbons, *supra* note 53, at 1356.

[56] HSIANG-CHING KUNG ET AL., DEATHS: PRELIMINARY DATA FOR 2005, CENTERS FOR DISEASE CONTROL, NATIONAL CENTER FOR HEALTH STATISTICS, *available at* http://www.cdc.gov/nchs/products/pubs/pubd/hestats/prelimdeaths05/prelimdeaths05.htm (last visited Aug. 12, 2008).

enhanced suicide warnings were issued did not lead to an increase in child and adolescent suicides.[57] Moreover, while Gibbons purports to show an association between a spike in suicides in 2003 and 2004 and alleged reductions in prescriptions for SSRI's, his own data reveals that there was virtually no reduction in prescriptions for the drugs studied during that period.[58] Instead, the reductions began in 2004, the year FDA ordered the black-box warning. *Id.*

Fish and Pregnancy

Fish is not a prescription drug. It has no warning label and does not need FDA approval or a doctor's prescription before it can be served to any willing diner *en papillote*. Likewise, *What to Expect When You are Expecting*[59] is not a peer-reviewed scientific journal usually relied upon by practitioners for medical information. Third, food contamination has

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[57] Benedict W. Wheeler et al., *The Population Impact on Incidence of Suicide and Non-fatal Self Harm of Regulatory Action Against the Use of Selective Serotonin Reuptake Inhibitors in Under 18s in the United Kingdom: Ecological Study*, 336 BMJ 515, 516 (2008), *available at* http://www.bmj.com/cgi/content/abstract/bmj.39462.375613.BEV1.

[58] Gibbons, *supra* note 51, at 1359; Jon N. Jureidini, Letter to the Editor, *The Black Box Warning: Decreased Prescriptions and Increased Youth Suicide?*, 164 AM. J. PSYCHIATRY 1907 (December 2007) (criticizing the Gibbons' study as flawed and misleading).

[59] WLF/ACEP Brief at 18.

nothing in common with risks inherent in prescription drugs. As the result, public advisory warnings related to any of these things have no relevance to preemption of failure-to-warn claims or arguments that "overwarning" doctors justifies it. *Id.* In fact, even if every failure-to-warn claim were preempted, it would do nothing to prevent another fish "scare" of this sort.

This and the following two examples demonstrate only that well-informed medical professionals are the best defense against public panics. Moreover, it shows that direct-to-consumer medical advice, including the kind contained in self-help books and drug industry advertising, can sometimes be misleading and harmful to patient safety.

Contraceptives and Abortion Rates

Industry *amici* next attempt to illustrate alleged overwarning by highlighting "Dear Doctor" letters issued by British, but not American, health authorities that allegedly caused British women to "suddenly stop taking their [birth control] pills," even though these letters did not advise them to do so, "because they

panicked."[60] Industry *amici* then claim a link to increased abortion rates in Europe.[61]

Preemption will not prevent the filing of the citizen petition that caused FDA to have to consider the matter, even though it took no action.[62] FDA and the drug industry will still have to deal with the same assertions of statutory and First Amendment rights by others that they themselves assert. Preemption will also not cure the patient non-compliance and public panic described nor did either result from pressure from litigation. Finally, unintended pregnancies and resulting abortions have many causes. Lawsuits regarding drug labels are not one of them.

Thimerisol and Measles Vaccine

The final "example" of alleged overwarning and litigation driving drugs from the market is a particularly inappropriate one.[63] Thimerisol is not a

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[60] *Id.* at 22 (quoting L. Dillner, *Pill Scare Linked to a Rise in Abortions*, 312 BMJ 996 (1996)).

[61] WLF/ACEP Brief at 22.

[62] *See id.* at 20; *and* 21 C.F.R. § 10.30 (2008).

[63] National Childhood Vaccine Injury Act of 1986, 42 U.S.C. §§ 300 aa1-34 (2006) (sets up no-fault system for processing vaccine claims).

prescription drug.[64] Instead, it is a preservative used when vaccines are dispensed in multi-dose vials.[65] Moreover, even the sources *amici* cite do not suggest that failure-to-warn claims caused the thimerisol "scare" or led to any measles outbreak. As the result, preemption would do nothing to prevent similar occurrences.

Bendectin and Pregnant Women

PhRMA/BIO claim that the anti-nausea drug Bendectin's removal from the market was the result of a scare initiated by *The National Enquirer* and allegedly unwarranted litigation that arose from it.[66] *The National Enquirer* is not yet a part of FDA nor does it play any role in drafting drug warnings. For these reasons, this is hardly a case of overwarning.

Nor do Bendectin lawsuits provide any justification for preemption. Even PhRMA admits the Bendectin experience is an isolated example.[67]

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[64] *See* U.S. FOOD & DRUG ADMINISTRATION, CENTER FOR BIOLOGICS EVALUATION AND RESEARCH, THIMERISOL IN VACCINES, *available at* http://www.fda.gov/Cber/vaccine/thimerosal.htm#t1 (last visited Aug. 12, 2008).

[65] *Id.*; *see also* 21 C.F.R. § 610.15(a) (2005).

[66] PhRMA/BIO Brief at 23.

[67] PhRMA's own spokesman admitted that Bendectin is the only drug ever withdrawn from the market solely because of bad publicity surrounding litigation. Gina Kolata, *Controversial Drug Makes a Comeback*, N.Y. TIMES, Sept. 26, 2000, at F-1.

Moreover, Bendectin is not really gone: its ingredients – vitamin B6 and the antihistamine doxylamine – are sold without a prescription. *Id.* Most important, if, as PhRMA/BIO seems to imply, these claims were scientifically baseless, the solution is not to preempt a whole class of claims entirely, but rather to take the much less draconian approach this Court outlined in *Daubert v. Merrell Dow Pharmaceuticals, Inc.*, 509 U.S. 579 (1993), which arose from Bendectin litigation, addressed the same issues PhRMA/BIO raises here, and established the legal threshold for admitting scientific evidence of causation. While medical *amici* agree that truly frivolous lawsuits do not belong in our legal system, their existence provides no reason to preempt all failure-to-warn claims, even meritorious ones.

Petitioner and its *amici* would have this Court stop the flow to doctors of the kind of critical drug safety information that has been withheld from the medical community in the past based upon the unfounded fear of overwarning in prescription drug labels. Weighing the relative risks of harm, as this Court must do, one commentator concluded:

> To justify the absolute protection from liability for withholding risk information from sophisticated physicians that preemption would provide on the chance that physicians may under-prescribe a dangerous drug requires much stronger

> support than the generalized concern of over-warning currently articulated.[68]

Because Wyeth's *amici* have done little more here than attempt to create the very kind of unwarranted public health panic over alleged overwarning that they purport to foreclose through preemption, this Court should reject "overwarning" as justifying preemption of failure to warn claims.

B. Prescription Drug "Underuse" Is Not Attributable to Failure-to-Warn Claims or Alleged "Overwarning"

To the extent Wyeth's *amici* have failed to demonstrate any overwarning problem in the prescription drug context by providing at least one instance of true overwarning in any prescription drug label, they cannot succeed in blaming the alleged underuse of prescription drug on overwarning. Nevertheless, WLF/ACEP devote an entire section of their brief to the notion that "recent scientific and medical studies confirm the adverse public health consequences of overwarning" and argue that prescription drug underuse is just such a consequence.[69] Even a cursory review of the studies cited reveals, however, that none support the notion

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[68] Davis, *supra* note 26, at 1143.

[69] WLF/ACEP Brief at 13.

that alleged "overwarning" attributable to litigation is any factor in the alleged underuse of prescription drugs. Instead, the cited studies conclude that misperceptions in the public domain or lack of knowledge on the part of physicians, patients, and pharmacists caused the alleged underuse of prescription drugs. In fact, none of the listed studies cite to, quote from, or reference any FDA-approved labeling for any prescription medication, nor do they mention tort claims as a factor in causing underuse.

The Shrank study,[70] for example, found that, while underuse of medications was a significant problem in pharmacologic care, even greater problems were found in "education and documentation" and "appropriate medication monitoring processes." *Id.* Thus, the study says no more than that there are several aspects to the allegedly substandard prescribing practices of physicians in America, one of which is underuse of medications. It says nothing to support the notion that alleged "overwarning" resulting from tort lawsuits is an impediment to the delivery of appropriate pharmacologic care to patients.

While industry *amici* suggest that "medical researchers in peer-reviewed publications repeatedly have pointed to unfounded safety concerns as a driving

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[70] William H. Shrank et al., *The Quality of Pharmacologic Care for Adults in the United States*, 44 MEDICAL CARE 936, 940 (2006).

factor" in drug underutilization,[71] the Gutierrez[72] study does not hint that such misperceptions are the result of overwarning in prescription drug labels. Instead, it observes that "It is not known why ß-Adrenoceptor Antagonists are not universally prescribed enough despite compelling evidence for their use in patients with coronary disease." It then posits that "many have reasoned that physicians . . . are reluctant to give ß-Adrenoceptor Antagonists because of what they perceive as absolute contraindications . . ." *Id.* It does not, however, attribute such perceptions to anything found in a prescription drug label. Instead, the study ascribes alleged underuse to misperceptions or misinformation in physicians' general knowledge base.

WLF/ACEP also cites Wenzel,[73] who focused on ***pharmacists'*** and ***patients'*** knowledge of drug risks and urges patient education. *Id.* at 642. There is nothing in his article to suggest that alleged underutilization of drugs is the result of tort claims or alleged overwarning in prescription drug labels.

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[71] WLF/ACEP Brief at 14-15.

[72] Michael A. Gutierrez et al., *Underutilization of ß-Adrenoceptor Antagonists Post-Myocardial Infarction*, 5 AM. J. CARDIOVASC. DRUGS 23, 27 (2005).

[73] Richard Wenzel, *Migraine Headache Misconceptions: Barriers to Effective Care*, 24 PHARMACOTHERAPY 638, 641 (2004).

Finally, WLF/ACEP cite Koren and Levichek[74] who also conclude that misperceptions and misinformation in the public domain about anti-nausea drug risks in pregnancy is an impediment to its appropriate use.[75] Nothing in their study attributes this confusion to tort litigation or alleged overwarning. Instead, even FDA has admitted that its pregnancy category labeling is outmoded and inadequate. For that reason, it proposed "major revisions" in May 2008, long after the article cited was published, "to provide more complete information about the effects of medicines used during pregnancy and breast-feeding."[76]

In short, Wyeth's *amici* cannot show any connection between alleged overwarning and alleged prescription drug underuse because there is not one.[77] The mere unfounded fear of alleged overwarning and

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[74] Gideon Koren et al., *The Teratogenicity of Drugs for Nausea and Vomiting of Pregnancy: Perceived Versus Real Risk*, 186 AM. J. OBSTET. GYNECOL. 5248, 5252 (2002)

[75] WLF/ACEP Brief at 15.

[76] *See* U.S. FOOD & DRUG ADMINISTRATION, CENTER FOR DRUG EVALUATION AND RESEARCH, PREGNANCY AND LACTATION LABELING (May 28, 2008), *available at* http://www.fda.gov/cder/regulatory/pregnancy_labeling/default.htm.

[77] *See, e.g.*, Michael A. Steinman et al., *Polypharmacy and Prescribing Quality in Older People*, 54 J. AM. GERIATRICS SOC. 1516 (2006) (study concluding that alleged drug under- and overuse occur at similar rates).

resulting underuse of prescription drugs cannot justify preempting all failure-to-warn claims, leaving injured patients in the cold, and doctors in the dark.

CONCLUSION

This brief ends as it began: with the Hippocratic oath. In its spirit, *Amicus,* the California Medical Association, ask that this Court do no harm and affirm the decision of the Vermont Supreme Court.

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BRIEF OF DANIEL PAUL CARPENTER, AARON S. KESSELHEIM, JERRY AVORN, MARC T. LAW, AND DANIEL POLSKY AS *AMICI CURIAE* SUPPORTING RESPONDENT

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INTEREST OF AMICI CURIAE

Amici are professors who teach and write on the politics and economics of pharmaceutical regulation and physician-researchers who study prescription-medication use and policy.[1] *Amici* wish to ensure

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[1] Pursuant to Supreme Court Rule 37.6, counsel for the *amici* certifies that this brief was not authored in whole or in part by counsel for any party, and that no person or entity other than the *amici* or their counsel has made a monetary

that the Court fully considers the social costs and benefits associated with the Vermont Supreme Court's holding in this case. *Amici* have no stake in the outcome of this case. They are filing this brief as individuals and not on behalf of the institutions with which they are affiliated.

Daniel Paul Carpenter is the Allie S. Freed Professor of Government, Faculty of Arts and Sciences, Harvard University. Before joining the faculty at Harvard, he taught political science at Princeton University and the University of Michigan. He is author of the book The Forging of Bureaucratic Autonomy: Networks, Reputations and Policy Innovation in Executive Agencies, 1862-1928 (Princeton University Press 2001), and a book manuscript, Reputation and Power: Organizational Image and Pharmaceutical Regulation at the FDA (forthcoming, Cambridge University Press or Princeton University Press). He has written numerous technical and statistical articles on drug regulation, including Drug Review Deadlines and Subsequent Safety Problems, 358 New Eng. J. Med. 13:1354 (2008) (with Evan James Zucker and Jerry Avorn); Regulatory Errors with Endogenous Agendas, 51 Am. J. Pol. Sci. 4:835 (2007) (with Michael Ting); Protection Without Capture: Product Approval by a Politically Responsive, Learning Regulator, 98 Am. Pol. Sci. Rev. 4:613 (2004); Staff Resources Speed FDA Drug Review, 29 J. Health, Pol. Pol'y & L. 3 (2004); The Political Economy of FDA Drug Approval: Processing, Politics and Lessons for Policy, 23 Health Affairs 1:52 (2004); and Groups,

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contribution to the preparation or submission of this brief. Pursuant to Rule 37.3(a), letters of consent from both parties to the filing of this brief have been filed with the Clerk.

the Media, Agency Waiting Costs, and FDA Drug Approval, 46 Am. J. Pol. Sci. 3:490 (2002). Professor Carpenter has also written on the legislative history of the 1938 Food, Drug and Cosmetic Act in Policy Tragedy and the Emergence of Regulation: The Food, Drug and Cosmetic Act of 1938, 21 Stud. in Am. Pol. Dev. 2:149 (2007) (with Gisela Sin). He earned a Ph.D. in political science from the University of Chicago.

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approval process, and the costs and availability of therapeutic entities both domestically and in resource-poor settings. He has also investigated how other legal issues affect the American health care system, including expert testimony in malpractice cases, health care fraud, and insurance reimbursement practices. He is a member of the New York State Bar and is a patent attorney.

Jerry Avorn is a professor of medicine at Harvard Medical School and chief of the Division of Pharmacoepidemiology and Pharmacoeconomics at Brigham and Women's Hospital. An internist, geriatrician, and drug epidemiologist, he studies the intended and adverse effects of drugs, physician prescribing practices, and medication policy. He has served on several national and international panels as an expert on the determinants and consequences of medication use and is a past president of the International Society for Pharmacoepidemiology. Dr. Avorn has authored more than 200 papers in the medical literature on medication use and its outcomes and been named one of the most highly cited researchers in the area of medicine and the social sciences. His book, Powerful Medicines: The Benefits, Risks, and Costs of Prescription Drugs, was published in 2004 by Knopf. He graduated from Columbia University, earned an M.D. from Harvard Medical School, and completed his training and certification in internal medicine within the Harvard teaching hospital system.

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SUMMARY OF ARGUMENT

Amici support the view of respondent and the Vermont Supreme Court that Congress has not chosen to preempt state-law failure-to-warn litigation. Economists writing in support of petitioner Wyeth (Petitioner's Economists) have asserted that the lack of preemption imposes heavy

social costs. Br. of J.E. Calfee et al. [hereinafter Economists' Br.]. That assertion is wrong. Empirical data and correct analysis demonstrate instead that Congress's refusal to foreclose state litigation has important social benefits.

State-law failure-to-warn litigation plays an essential role in promoting drug safety. Significant imbalances of safety-related information are inherent in the approval of pharmaceutical products. State-law failure-to-warn litigation mitigates that information asymmetry because it aligns the incentives of drug manufacturers and consumers by: (1) supplementing the FDA's inadequate resources and incentives to monitor comprehensively the performance of every drug on the market, (2) providing a strong incentive to drug manufacturers to change labeling unilaterally to respond to signals of health risks associated with their products, and (3) providing consumers with recourse in the event that drug manufacturers do not strengthen warnings about their products when appropriate.

State-law failure-to-warn litigation does not, as erroneously contended by Petitioner's Economists, exacerbate a perceived problem with the FDA's being overly cautious in drug approvals and labeling. In fact, such litigation provides incentives for the FDA to approve more drugs than it otherwise would and approve them more expeditiously.

Petitioner's Economists badly misconstrue the FDA's capabilities and incentives, and they ignore the notion that incentives for drug manufacturers to maximize profits may be misaligned with the ideal outcomes for public health. Petitioner's Economists incorrectly assume that the FDA is privy to perfect information, capable of enforcing its agenda with

the same level of authority before and after a drug is approved for the market, and monolithically incentivized to protect its reputation above all else by exercising undue caution. All three of those assumptions are incorrect. Information asymmetries, budget inadequacies, and regulatory realities limit the FDA's ability to enforce a concerted agenda, if it had one. Moreover, there are significant pressures on the FDA—from drug companies, patient advocates, members of Congress, the media, even investors in pharmaceutical companies—to approve drugs quickly, even if those drugs also may have potentially dangerous side effects. Further, even if the premise that FDA drug-approval policy is too risk-averse were not faulty, nothing supports Petitioner's Economists' treatment of the FDA's *labeling* policy as indistinguishable from its allegedly overcautious approval policy.

Nor is it correct to assume that the FDA can continuously optimize its regulatory standard throughout a drug's lifecycle. In reality, the FDA's tools for gathering post-approval information are relatively crude and ineffective, meaning the quality of information that the FDA receives for drugs once they reach the market may be severely limited. Crucial information about a drug's safety may become available only as a direct result of failure-to-warn litigation. And, after a drug is approved, FDA authority to compel labeling changes or further studies is substantially reduced. The lack of high-quality information and the limits on FDA enforcement power severely undermine the FDA's ability to act as an effective regulator of what physicians and patients know about a drug once it is on the market. Accordingly, the tort system encourages manufacturers to act reasonably in

warning physicians and patients about newly emerging risks and helps ensure that important risk information is provided to physicians, patients, and the FDA.

ARGUMENT

I. STATE FAILURE-TO-WARN LITIGATION PLAYS A CRITICAL ROLE IN PROMOTING DRUG SAFETY.

State failure-to-warn lawsuits are critical to promoting drug safety, particularly with respect to the level of precaution undertaken by drug manufacturers in how they present information about adverse events to physicians and patients. The contributions of tort law to product safety were recognized early on by leading thinkers of the law and economics movement, especially those associated with the Chicago School of economics.[2] The safety and efficiency benefits of state-law failure-to-warn suits are precipitated by a nuanced array of economic

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[2] See Landes et al., A Positive Economic Analysis of Products Liability, 14 J. Legal Stud. 535, 566 (1985) (concluding that "the economic structure of the common law of products liability . . . is in the main economically rational, much as [their] other studies have found with regard to other, and somewhat less controversial, areas of tort law and of the common law more broadly"); Landes et al., Tort Law as a Regulatory Regime for Catastrophic Personal Injuries, 13 J. Legal Stud. 417, 434 (1984) ("In view of the many criticisms that have been leveled against regulation, it would be a shame to give up on tort law as a method of regulating safety in cases of catastrophic accident without careful consideration of its actual and potential resources as a system of safety regulation."); Shavell, A Model of the Optimal Use of Liability and Safety Regulation, 15 RAND J. Econ. 271, 271 (1984) ("[N]either liability nor regulation is necessarily better than the other, and as is stressed, their joint use is generally socially advantageous.").

and structural forces, but all those forces are tied together by two fundamental concepts: incentives and information. The recourse provided by state failure-to-warn suits helps align producer incentives with consumer safety concerns and ensure that consumers have optimal information so that market transactions are more apt to be based on mutually beneficial exchanges between consumers and producers.

A. Failure-to-Warn Litigation Serves a Supplementary Administrative Function to Improve Oversight of Drug Safety Because Pharmaceutical Manufacturers Are in the Optimal Position to Identify Emerging Safety Concerns.

When a drug is approved by the FDA, it is approved based on a small number of studies in a modest number of subjects, some of whom may be disease-free volunteers and many of whom are far healthier than the patients for whom doctors usually write prescriptions. These studies may last only a brief time, sometimes as short as eight to sixteen weeks, even for drugs designed to be taken for a lifetime. This is possible because the effect that forms the basis for approval may be improvement of a laboratory test (*i.e.*, a surrogate marker) rather than real clinical outcomes. But requiring a drug to be studied in many thousands of patients over many years before approval could delay important new products from entering the market. Should FDA Drug and Medical Device Regulation Bar State Liability Claims? Hearing Before the H. Comm. on Oversight and Government Reform, 110th Cong. (2008) (statement of Aaron S. Kesselheim, Div.

of Pharmacoepidemiology and Pharmacoeconomics, Brigham and Women's Hosp., Harvard Med. Sch.).

As a result, when the FDA approves a drug, it cannot fully certify its ongoing safety. *E.g.*, A Guide to Drug Safety Terms at FDA, April 11, 2008, http://www.fda.gov/consumer/updates/drugterms041108.html ("[E]ven with a rigorous evaluation process, some safety problems surface only after a drug has been on the market and has been used in a broader population."). Indeed, studies show that half of all drug withdrawals occur within two years after the drug was first approved. Lasser et al., Timing of New Black Box Warnings and Withdrawals for Prescription Medications, 287 J. Am. Med. Ass'n 2215, 2215 (2002). The FDA has two significant limitations that impede its ability to assure drug safety after a product is approved. First, as noted above, during the approval process, the manufacturer's clinical tests necessarily involve only a limited sample of patients and are often statistically powered to detect changes in clinical endpoints, rather than important adverse events that might arise. Thus, the FDA may not have a complete picture of the safety of drugs being considered for approval—and some rare side effects may escape detection altogether. See Kessler et al., A Critical Examination of the FDA's Efforts to Preempt Failure-to-Warn Claims, 96 Geo. L.J. __, __ (2008) (forthcoming) [hereinafter Kessler, A Critical Examination] ("[P]re-approval testing generally is incapable of detecting adverse effects that occur infrequently, have long latency periods, or affect subpopulations not included or adequately represented in the studies (*e.g.*, the elderly, ethnic minorities and pregnant women)."). Second, as has been widely recognized for decades, the post-

marketing safety functions of the FDA have been severely underfunded, sharply reducing the effectiveness of such activities. The FDA thus, after approval, lacks the resources and capability to actively monitor evolving knowledge about a drug. *Id.*, at ____; J. Avorn, Powerful Medicines: The Benefits, Risks, and Costs of Prescription Drugs 36 (2004) [hereinafter Avorn, Powerful Medicines].

The FDA often cannot uncover the latent risks of approved drugs, or would have to incur significant expenses—for which it does not have the budget—to do so.[3] Those discovery costs effectively limit the extent to which the FDA can ensure that the drug labels it approves when the drug is first marketed continue to warn consumers effectively about the potential consequences of a given treatment. Avorn, Powerful Medicines 169.[4]

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[3] An example of this issue surfaced in litigation relating to Zyprexa, a drug manufactured by Eli Lilly to treat schizophrenia and bipolar disorder that has also been linked to serious side effects like severe weight gain, increases in cholesterol and blood sugar, and diabetes. Berenson, Lilly Settles With 18,000 Over Zyprexa, N.Y. Times, Jan. 5, 2007, at C1 (discussing documents showing that "Lilly played down the risks of Zyprexa to doctors as the drug's sales soared after its introduction in 1996").

[4] See also Kessler et al., *supra*, at 8 ("The FDA's statutory and regulatory tools for gathering post-approval information are relatively crude and often ineffective, especially when contrasted with its tools for information gathering prior to approval. For that reason, the tort system has historically provided important information about these newly-emerging risks to physicians, patients and the FDA."). The 2007 FDA Amendments Act gave the FDA somewhat heightened authority to require postmarketing studies, Pub. L. No. 110-85, §901 et seq., 121 Stat. 823 (2007), but the FDA still has to know enough about the potential risk associated with a given drug to ask for

Pharmaceutical manufacturers, however, closely monitor the use of their products after FDA approval, organize postmarketing studies, and analyze voluntary spontaneous reports from physicians and other sources about adverse events arising in the course of therapy. Pharmaceutical manufacturers' sales representatives maintain frequent contact with physicians and hospitals to promote use of their products. The manufacturer is thus in the best position to learn about emerging safety concerns. By law, drug manufacturers are required to submit periodic reports of adverse events in certain categories relating to their products, 21 CFR §§310.305, 314.80 (2007), but the way pharmaceutical companies choose to define or fill out those categories may omit or underrepresent clinically significant safety problems.

Manufacturers often have considerable latitude regarding whether to study or not study a given adverse effect in the post-marketing setting, and even in the measurement and analysis of the safety data available to them. When safety issues emerge that suggest limiting the scope of use, or removing a drug from the market altogether, some pharmaceutical companies have chosen to downplay reports of side effects and obfuscate their periodic reports to the FDA. Psaty et al., Reporting Mortality Findings in Trials of Rofecoxib for Alzheimer Disease or Cognitive Impairment, 299 J. Am. Med. Ass'n 1813, 1814-1815 (2008); Psaty et al., Potential for Conflict of Interest in the Evaluation of Suspected Adverse Drug Reactions: Use of Cerivastatin and Risk of Rhabdomyolysis, 292 J. Am. Med. Ass'n

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these studies. It is too soon to determine how effective these measures will be.

2622, 2626-30 (2004). That conduct occurs because providing new safety information quickly and accurately to the FDA may cause the agency to recommend adding new warnings to the official label, or to remove the drug from the market altogether. Thus, use of the product might be reduced (or eliminated), and the manufacturer's profits will fall. Manufacturers have a duty to their shareholders to maximize profits.

State failure-to-warn litigation provides substantial penalties for manufacturers' decisions to hide or downplay reports of safety issues that emerge after a product reaches the market. Potential damage awards provide drug manufacturers with a strong incentive to expeditiously provide full and clear information to physicians and the FDA that otherwise may not come to light. Without such litigation, drug manufacturers would have a stronger incentive to act in their immediate financial interest and be less forthcoming in providing emerging safety-related data.

State tort lawsuits thus provide an incentive for drug manufacturers to fully disclose their knowledge of product risks to the FDA, improving its ability to strike the correct balance between Type I errors (failing to require a warning when that warning is necessary) and Type II errors (requiring a warning when that warning is not necessary). Further, state failure-to-warn suits encourage drug manufacturers to work with the FDA to ensure that labels accurately reflect the risks associated with a given treatment. Given the potential ambiguity and biased judgment calls inherent in drug risk assessment, the well-documented problems with companies' reporting of adverse events to the FDA, and the agency's

limited capacity to analyze the safety data it receives, state failure-to-warn suits are necessary to supplement the FDA's regulatory mission. As full information is critical to enabling physicians and patients to make the best possible decisions about medication use, such suits play a vital role in optimizing social welfare.

B. Failure-to-Warn Litigation Provides an Additional Deterrent Function Helping Promote Drug Safety by Encouraging Drug Manufacturers to Change Labeling Unilaterally to Respond to Risks.

State tort suits provide an additional incentive that complements the FDA—a deterrent mechanism that federal agencies like the FDA cannot replicate. The availability of state failure-to-warn litigation helps protect consumers when harmful consequences become apparent regarding drugs that have already been approved by the FDA. When such information becomes apparent to manufacturers and not the FDA, as is usual, manufacturers may not act appropriately with that information.

In the past, manufacturers have continued to promote their products to physicians and have engaged in strategies to downplay emerging safety concerns. See Berenson, For Merck, the Vioxx Paper Trail Won't Go Away, N.Y. Times, Aug. 21, 2005, at 3 ("Merck sales representatives [were] trained to view doctors' concerns about Vioxx's heart risks as 'obstacles' to be avoided or dismissed. Another marketing document taught representatives to play 'Dodgeball' when doctors voiced concerns."). Those efforts have been intended to induce consumers to continue using drugs that the manufacturer knows

have emerging underreported or unreported risks. Without failure-to-warn litigation, consumers would have no recourse in the event that aggressive marketing induced them or their prescribing physicians into sub-optimal behavior because the FDA has no mechanism for awarding damages. Physicians cannot act as learned intermediaries in assessing the risk-benefit profile of a drug if they do not have adequate risk information.

State tort lawsuits create the potential for losses (in the form of damages payments) in the face of corporate malfeasance. If the FDA were the only force regulating the drug market, drug manufacturers would have an incentive to exploit their information advantage to continue to promote drugs with important safety problems without proper warning. Given the immense power of the profit motive, a drug manufacturer could have strong incentives to sell a drug it knows to have underreported harmful consequences to recoup its investment and meet the demands of stockholders. Even under the current system, there is evidence that some drug manufacturers have attempted to hide information from the FDA to get approval to market their drugs. See, *e.g.*, *In re Baycol Prods. Litig.*, 218 F.R.D. 197 (D. Minn. 2003); *In re W. Va. Rezulin Litig.*, 585 S.E.2d 52, 58-59 (W. Va. 2003). Reducing the cost of concealing information (which would occur if state tort liability were removed) would encourage drug manufacturers to withhold critical safety information more often. Failure-to-warn litigation thus encourages manufacturers to advertise their products accurately and fairly.

The net effect of this complementary arrangement is the promotion of full and accurate

knowledge about drug risks and the minimization of misstatements or error in drug labeling. A significant literature chronicles the social welfare benefits of dual regulation of risky technologies.[5] For example, Professor William Buzbee of Emory University explains that "[t]he common law system's independence and private incentives to challenge the status quo are particularly valuable antidotes to complacency and ineffective regulation." Buzbee, Asymmetrical Regulation: Risk, Preemption, and the Floor/Ceiling Distinction, 82 N.Y.U. L. Rev. 1547, 1556 (2007). Accordingly, state-law failure-to-warn litigation serves as a valuable complement to FDA regulation.

C. By Harnessing the Forces of Decentralization, Failure-to-Warn Litigation Expedites the Diffusion of New and Potentially Vital Information on the Characteristics of New Drugs.

State tort-liability suits serve an essential role in facilitating the rapid transmission of information about drugs' properties. Given the decentralized nature of the court system, civil tort trials can help reveal the unexpected effects of drugs after they have been approved by the FDA by providing individuals with local recourse. As the FDA has limited scope and ability to evaluate drugs after they have gained approval, state tort liability suits play an extremely important role in ensuring that drugs on the market

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[5] See generally Landau, Redundancy, Rationality, and the Problem of Duplication and Overlap, 29 Pub. Rev. 346 (1969); J. Bendor, Parallel Systems: Redundancy in Government (1985); C.F.L. Heimann, Acceptable Risks: Politics, Policy, and Risky Technologies (1997); Ting, A Strategic Theory of Bureaucratic Redundancy, 47 Am. J. Pol. Sci. 274-292 (2003).

are safe and properly labeled. Litigation brought by individual patients can help uncover previously unavailable data on adverse effects, questionable practices by manufacturers, and flaws in regulatory systems. Kesselheim and Avorn, The Role of Litigation in Defining Drug Risks, 297 J. Am. Med. Ass'n 308 (2007).

Furthermore, by forcing labeling issues under the microscope of the adversarial system, courts subject drugs to a powerful form of information gathering apart from the regulatory process. Indeed, the immense value of the adversarial system in gathering information that even a centralized body of experts might miss is a philosophical pillar of the U.S. court system. See, *e.g.*, Bernstein, Expert Witnesses, Adversarial Bias, and the (Partial) Failure of the Daubert Revolution, 93 Iowa L. Rev. 451, 457, n.28 (2008). Finally, the court system harnesses the power of market forces to catalyze the dissemination of information. Plaintiffs' failure-to-warn suits give lawyers an economic incentive to gather information that national regulatory bodies lack.

Conversely, the nontrivial costs of bringing a failure-to-warn suit acts as an additional filter on the legitimacy of the cases brought before the court as plaintiffs' attorneys will not recoup their investment if they undertake cases without a reasonable hope of success. FDA decisions and pronouncements can also play a significant role in juries' evaluation of failure-to-warn cases. Kessler, A Critical Examination, at __ (noting that a "drug company would have a powerful defense" when it is "able to argue to the jury that it complied with applicable FDA requirements and that the plaintiff is complaining about the absence of a

warning the FDA had rejected").[6] As unencumbered dissemination of information is key to effective safety regulation, state tort liability suits serve a vital economic function. Thus, while the FDA serves as the initial regulator of drug labeling, the state tort system plays a crucial role in assessing the FDA's errors and oversights.

II. PETITIONER'S ECONOMISTS FAIL TO DEMONSTRATE THAT PREEMPTION WOULD BE PREFERABLE TO PERMITTING STATE FAILURE-TO-WARN LITIGATION.

Petitioner's Economists attempt to show that Congress's decision not to preempt state failure-to-warn claims decreases social welfare by exacerbating error in the drug-labeling process. Their argument boils down to a three-step theory: (1) the FDA is overly cautious in drug *approval* because of political—specifically, reputational—pressures, (2) the FDA faces the same pressures and exercises the same excess caution in drug *labeling*, and (3) additional deterrence from state tort litigation exacerbates the detrimental effects from that excess caution. All of those steps are rebutted by empirical evidence and analysis.

A. A Framework for Evaluating the Types of Error and Social Costs at Issue

The costs at issue are those associated with two types of error. A Type I error would involve

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[6] As discussed further below, Petitioner's Economists completely ignore the potential symbiotic relationship between FDA regulation and litigation that has been documented in the relevant economic literature and write as though each process is performed without reference to the other.

approving a drug that should not have been approved or failing to require labeling verbiage when that verbiage is necessary; the associated cost is the decline in a patient's well-being from taking a drug that should not have been approved or taking an approved drug in the absence of critical warnings or contraindications.[7] A Type II error would involve failure to approve a beneficial drug or imposing verbiage that is not necessary; the associated cost is the decline in a patient's well-being resulting from *not* taking the drug because it was not approved or because of superfluous information ("overwarning"). The socially optimal approval or labeling standard is one that perfectly balances the expected cost of Type I errors and Type II errors.

To visualize the FDA's labeling calculus, think of the FDA assigning a probability that a given drug d (for example, Vioxx) causes a certain symptom s (for example, myocardial infarction) as P_{ds}. Let $Þ_s$ be the percentage of the general population that suffers from symptom s. Let P_{FDA} ($P_{FDA} > Þ_s$) be the "critical value" such that, when any drug-symptom pair is assigned a probability above P_{FDA}, the FDA requires the drug manufacturer to include verbiage relating to that drug-symptom pair (for example, "Vioxx may lead to myocardial infarction") on the drug's label.

Let P^* be the socially optimal labeling standard. In the absence of any biased political influence, P_{FDA} would be chosen so as to optimally balance the expected costs of Type I and Type II errors—that is, $P_{FDA} = P^*$.

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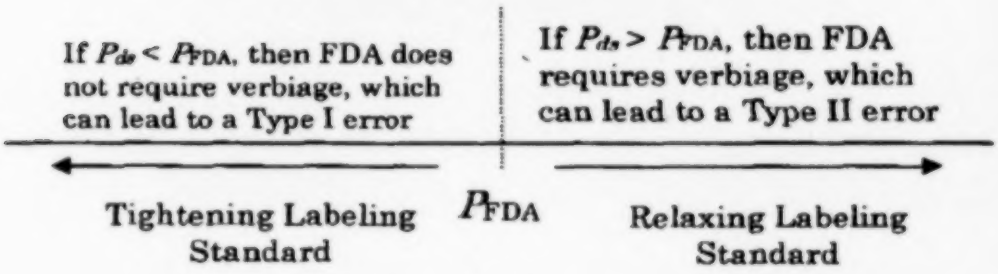
[7] A contraindication is a factor that makes use of a drug or medical procedure inadvisable.

When the FDA requires the drug manufacturer to include verbiage relating to a drug-symptom pair on the label, it exposes the patient to the possibility of a Type II error. Similarly, when the FDA does *not* require the drug manufacturer to include verbiage relating to a drug-symptom pair on the label, it exposes the patient to the possibility of a Type I error. As illustrated in Figure 1, as the FDA makes its labeling standard more stringent (that is, as P_{FDA} is moved to the left in the diagram), the probability of a Type I error is lessened and the probability of a Type II error is increased.

FIGURE 1: ERRORS AND COSTS ASSOCIATED WITH THE FDA'S LABELING STANDARD



A similar diagram could depict the issues facing the FDA in drug-approval decisions. Petitioner's Economists begin with the (untenable) premise that, in its drug-approval decisions, the FDA, due to political pressure, picks some critical value of P_{FDA} such that the balancing of error costs is suboptimal. In particular, they assert that the FDA tolerates too many Type II errors, causing $P_{FDA} < P^*$. They then leap to the assumption that the same situation prevails with regard to the FDA's drug-labeling decisions. Because there is no empirical or analytical support for those premises, nothing supports Petitioner's Economists' ultimate conclusions that

jury decisions in state failure-to-warn litigation exacerbates the problems caused by an overly cautious approach at the FDA and that preemption would thus provide an important safeguard against Type II errors.

B. There Is No Reason to Believe the FDA Is Overly Cautious in Labeling Standards.

Petitioner's Economists inaccurately ascribe motives to the FDA, making their conclusion that the FDA is unduly cautious when it comes to warning about drug safety concerns erroneous. In fact, the limited efficacy of the FDA as a regulatory body *after* a drug has been released to the market renders the FDA's incentives of ancillary importance.

1. There Is No Proof That the FDA Is Overly Cautious in Its Labeling Policy.

Petitioner's Economists repeatedly conflate the FDA's alleged *drug-approval* problem with its alleged *drug-labeling* problem, essentially treating the two issues as identical. As discussed further below, nothing supports the idea that today's FDA is overly cautious in drug approval. More germane to this case, Petitioner's Economists provide no empirical support for the proposition that the FDA is overly cautious with respect to its labeling policy.

Petitioner's Economists fail to provide any empirical evidence that the FDA is overly cautious with respect to its labeling policy and the FDA's excessive caution there leads to an inefficient level of Type II errors. The single relevant law review article cited, co-authored by one of Petitioner's Economists and a senior-assistant counsel for litigation at

Bristol-Myers Squibb, reads more like an advocacy piece. Its policy prescription—preemption of state tort liability with certain exceptions—is largely based on two anecdotal examples (DPT and Bendectin) that purport to show that "tort liability can create perverse incentives that actually harm social welfare." Viscusi et al., Deterring Inefficient Pharmaceutical Litigation: An Economic Rationale for the FDA Regulatory Compliance Defense, 24 Seton Hall L. Rev. 1437, 1480 (1994). Bendectin, however, was removed from the market 25 years ago, and the DPT anecdote has nothing to do with product-labeling issues. *Id.*, at 1470 (identifying DPT litigation as raising "design defect challenges"). To support their claim that the FDA is overly cautious regarding product labeling, Petitioner's Economists cite only a footnote in the law review article, which merely restates the central claim in their amicus brief that the FDA is overly cautious in its labeling calculus (again without any empirical support). See *id.*, at 1469 n.118. Finally, even the law review article does not advocate *blanket* preemption of state tort liability relating to drug labeling—the position now advocated by Petitioner's Economists. Instead, the article advocates several important exceptions to preemption, including fraud on the FDA and uses of drugs in ways not approved by the FDA (*i.e.*, "off-label" uses), *id.*, at 1478, which can account for over 70% of the prescriptions in some drug classes.[8]

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[8] Off-label use is central to a case brought by ten state attorneys general against Eli Lilly involving the drug Zyprexa. The lawsuit accuses Lilly of "running an illegal marketing campaign to promote Zyprexa for unapproved off-label uses, including treating children," and alleges that Lilly's campaign concealed risks, including diabetes, weight gain, and

The only other piece of evidence presented by Petioner's Economists is a May 2008 newspaper article relating to a single anecdote, Label on Merck Vaccine to Disclose a Death, Wall St. J., May 2, 2008, at B8, that purports to show that the FDA required Merck to include superfluous information on a label for Rotateq (a vaccine). The FDA required Merck to report on its label the death of a recipient of the drug due to an intestinal obstruction. *Ibid.* A Merck spokesperson claimed that the "rate of reported cases of intestinal obstruction, or intussusception, hasn't been greater than expected by chance alone." *Ibid.* But that claim, even if true, does not constitute proof that the FDA systematically imposes a suboptimal labeling standard. Using the framework depicted in Figure 1, Merck is merely claiming that the critical value used by the FDA, P_{FDA}, is not significantly greater than the percentage of the population with intussusceptions, P_s. If the cost of a Type II error with respect to labeling policy is small relative to the cost of a Type I error, then the FDA's requirement that Merck include such verbiage may be consistent with the socially optimal (and very stringent) drug-labeling standard. Rotavirus vaccines have, in fact, been linked to intussusception in children, see, *e.g.*, Suspension of Rotavirus Vaccine After Reports of Intussusception—United States, 1999, 53(34) MMWR Weekly 786, Sept. 3, 2004, available at http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5334a3.htm, making the warning a clinically relevant issue.

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cardiovascular problems. See Tenth State Sues Over Eli Lilly Drug, Wall St. J., Mar. 12, 2008, at B4.

2. Petitioner's Economists Overstate the FDA's Incentives for Caution and Ignore Evidence of Pressure for Faster Drug Approval and FDA Risk-Taking.

Petitioner's Economists' conclusions about FDA drug-labeling policy proceed from assertions about its drug-approval policy that are simply not true. They claim that, due to political pressure, the FDA's risk aversion leads it to withhold beneficial therapies from the American health system. That assertion relies on studies twenty years old or older, written in the 1970s, when European regulatory agencies approved some drugs (for example, beta-blockers) years before the FDA did. Numerous later studies show that the FDA no longer lags other countries in approving new drugs.[9] Indeed, in recent decades, the U.S. is frequently the first country to approve a new drug. Since the Prescription Drug User Fee Act (PDUFA), 21 U.S.C. §301 et seq., was enacted in 1992, the FDA has been required to adhere to strict deadlines for drug approval and has markedly

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[9] *E.g.*, Kessler et al., Approval of New Drugs in the United States. Comparison with the United Kingdom, Germany, and Japan, 276 J. Am. Med. Ass'n 22:1826, 1826 (1996) ("The analysis reveals that the United States and the United Kingdom have similar patterns of drug availability, although the United States has a number of therapies with significant public health benefits that are not yet available in the United Kingdom. The findings also show that the United States outpaces both Germany and Japan in approving important new drugs."); see also Rawson, Time Required for Approval of New Drugs in Canada, Australia, Sweden, the United Kingdom, and the United States in 1996-1998, 162 Can. Med. Ass'n J. 4:501, 503-504 (U.S. approval times shorter than Sweden, Canada, and Australia).

accelerated its speed of decision-making. By contrast, there is little evidence of scientifically inappropriate delayed decisions (or outright rejections) of important new products that have kept useful therapies from the American public.

Regulatory agencies like the FDA do take their reputation into account, but reputation cuts both ways. There is substantial political criticism when the FDA delays or blocks introduction of a new drug. For example, when the first therapies for AIDS were developed, political activists, along with congressional committees and politicians from both major parties, pressured the agency to accelerate its drug-approval process. From 1986 to 1998, FDA drug-approval times fell from an average of 24-30 months to 12 months. P. Hilts, Protecting America's Health: The FDA, Business, and One Hundred Years of Regulation 278-279, (2003); Carpenter et al., Approval Times for New Drugs: Does the Source of Funding for FDA Staff Matter?, Health Affairs, Web Exclusive, W3-618-624, (2003) available at http://content.healthaffairs.org/cgi/reprint/hlthaff.w3.618v1 [hereinafter Carpenter et al., Web Exclusive]. In recent years, many politicians and activists have followed the AIDS-policy example and pressured the agency for quicker approvals and less stringent regulation of new therapies. Many newspaper editorial boards, including the Wall Street Journal, have joined this chorus. *E.g.*, Review & Outlook—Breast Cancer Reprieve, Wall St. J., Feb. 27, 2008, at A16; Review & Outlook—A Moral Test for the FDA, Wall St. J., Feb. 21, 2008, at A16.

Numerous empirical studies also show evidence of those patterns. They demonstrate a robust association between the strength of patient advocacy

groups and the speed of FDA drug approval. Controlling for the severity of the disease targeted by the drug, the greater the political organization of the patient advocates for the targeted disease, the faster the drug in question will be approved. Carpenter, The Political Economy of FDA Drug Approval: Processing, Politics, and Lessons for Policy, 23 Health Affairs 52, 56-60 (2004); see generally Carpenter, Groups, the Media, Agency Waiting Costs, and FDA Drug Approval, 46 Am. J. Pol. Sci. 3:490 (2002). Accordingly, in ignoring the potential for patient advocacy groups and other organized interests to lobby the FDA for faster drug approvals, Petitioner's Economists seriously overstate the FDA's incentive to be excessively cautious in drug-approval decisions.

The last two decades have also witnessed major policy changes—supported by the FDA and politicians in both major parties—that have significantly reduced drug-approval time and increased the degree of risk-taking on the FDA's part. The most notable change was PDUFA, first enacted in 1992 and subsequently reauthorized three times, most recently in 2007. Several studies, including one recent study by two of Petitioner's Economists, show that this law has accelerated FDA drug approval. See generally Carpenter et al., Web Exclusive; Berndt et al., Industry Funding of the FDA: Effects of PDUFA on Approval Times and Withdrawal Rates, 4 Nature Reviews Drug Discovery 545 (2005). Other studies show that the deadlines imposed by these changes are associated with highly abrupt approvals of new medicines and higher rates of postmarket safety problems for drugs once they reach the market. See generally Carpenter et al., Drug Review Deadlines and Subsequent Safety

Problems, 358 New Eng. J. Med. 13:1354 (2008). Additionally, there is evidence linking faster approval times with a higher incidence of adverse drug reactions. Olson, The Risk We Bear: The Effects of Review Speed and Industry User Fees on New Drug Safety, 27 J. of Health Econ. 175, 177 (2008); Olson, Pharmaceutical Policy Change and the Safety of New Drugs, 45 J.L. & Econ. 615, 632-641 (2002). That body of evidence suggests that Petitioner's Economists' characterization of the FDA as excessively cautious, acting too strongly in favor of minimizing Type I error in drug approval, is erroneous.

Petitioner's Economists' argument assumes both that reputational pressure is the overriding (or only) incentive acting on the FDA and that such pressure acts in only one direction. But, as the empirical data confirm, numerous incentives for rapid drug approval and risk-taking also face the agency, at least balancing any incentives for excess caution.

3. Petitioner's Economists Fail to Prove That the FDA's Labeling Policy Does Not Strike the Proper Balance Between Type I and Type II Errors.

Having failed to offer *any* convincing empirical proof that the FDA is overly cautious in its labeling policy, Petitioner's Economists rely entirely on economic theory to make their case. But their theory fails on at least two levels. First, Petitioner's Economists' premise that the FDA errs toward too many Type II errors in drug *approval* is flawed. Secondly, in any event, the sleight of hand by which they attribute the same alleged FDA risk aversion to its drug-*labeling* policy cannot withstand scrutiny.

Even if there were reason to believe that the drug-approval process produces suboptimal outcomes due to risk aversion, there is no basis for concluding that this effect permeates every decision made by the FDA. Indeed, there are no *a priori* reasons to believe that the FDA is excessively risk averse when it comes to regulating product labels because labels that are lacking pertinent information (Type I error) and labels that are so long as to obfuscate interpretation (Type II error) will both receive public scrutiny. The media, consumers, and consumer advocates have proven sensitive to allegedly overly stringent regulations.[10] The Wall Street Journal articles cited by Petitioner's Economists are perfect examples of bad press for the FDA when it requires too much verbiage. Hensley, Long Labels Help Drug Firms, But Can Obscure What Matters, Wall St. J., June 28, 2005; Hensley, Liability Worries Cloud Drug Labels, Wall St. J., July 5, 2005. Thus, Petitioner's Economists are wrong to argue that the FDA errs in the direction of Type II errors only.

Finally, Petitioner's Economists fail to consider the possibility that FDA staff and its advisory

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[10] The public is definitely aware of such Type II errors. For example, a 2006 New York Times article about antidepressants noted criticism by psychiatrists of the FDA's increased warning label requirements. An assistant professor of child psychiatry at Columbia University voiced strong concerns over whether more stringent labeling rules for antidepressants had caused a reduction in antidepressant prescriptions, which in turn could cause an increase in the suicide rate. Carey, Panel to Debate Antidepressant Warnings, N.Y. Times, Dec. 13, 2006, at A30. A 2004 New York Times article noted similar concerns by psychiatrists after the FDA imposed stricter antidepressant labeling rules. Harris, F.D.A. Toughens Warning On Antidepressant Drugs, N.Y. Times, Oct. 16, 2004, at A9.

committees are subject to regulatory capture by drug companies, which would cause staff to tolerate too many *Type I* labeling errors, that is, a bias in the opposite direction. A 2006 study in the Journal of the American Medical Association investigated the financial conflicts of interest at the FDA. See generally Lurie et al., Financial Conflict of Interest Disclosure and Voting Patterns at Food and Drug Administration Drug Advisory Committee Meetings, 295 J. Am. Med. Ass'n 1921 (2006). The study found that, at 73% of drug-related advisory committee meetings over a three-year period, at least one voting scientist present had disclosed a conflict yet only 1% of the advisory committee members were recused. *Id.*, at 1921. About a quarter of the conflicts involving consulting arrangements, contracts or grants, and investments exceeded $10,000, $100,000, and $25,000 respectively. *Ibid.* A "statistically significant positive relationship was apparent for competitor conflict" and voting patterns. *Ibid.*; see also Harris et al., 10 Voters on Panel Backing Pain Pills Had Industry Ties, N.Y. Times, Feb. 25, 2005, at A1. Depending on the severity of this classic regulatory-capture problem, the FDA may be imposing a labeling standard that is *too lenient* relative to the socially optimal standard—that is, $P_{FDA} > P^*$. If that were the case, then any alleged bias introduced by state tort liability would nudge the outcome of Type I and Type II errors toward the socially optimal level.

4. Petitioner's Economists Conflate the Costs of a Type II Error Associated with the FDA's Labeling Policy with Costs of a Type II Error Associated with the FDA's Drug-Approval Policy.

Petitioner's Economists argue that state-tort-law requirements "exacerbate FDA Type II errors" by causing drug manufacturers to "hold back on seeking approval of new drugs or to add defensive labeling." Economists' Br. 13. But they exaggerate the costs of a Type II error related to the FDA's *labeling* policy by drawing on the costs of such an error related to the FDA's *drug-approval* policy. Stated differently, Petitioner's Economists, when attempting to emphasize the possible social costs of Type II errors relating to labeling policy, cannot avoid invoking dynamic effects ("holding back on seeking approval") associated with the FDA's drug-approval policy.

Of the five social costs Petitioner's Economists describe as associated with an "added layer of tort liability overdeterrence," *id.*, at 14, the first two—limited drug availability and disincentives for research and development—*have no connection with the FDA's labeling policy*, and should therefore be ignored here.[11] When considering the Type II error costs associated with the FDA's labeling policy, the only relevant cost to consider in their five-part

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[11] Arguably, it is possible that lost sales due to overwarnings could adversely affect a drug manufacturer's profits. But Petitioner's Economists do not make that argument, and no evidence exists that such overwarnings generate sufficiently material losses to induce exit by drug manufacturers.

list is item 4, "Defensive Labeling." *Id.*, at 17.[12] Petitioner's Economists correctly point out that the primary costs associated with defensive labeling relate to overwarning, *i.e.*, discouraging beneficial use of drugs. Petitioner's Economists do not quantify those error costs, and, although it is possible that such costs are economically significant—perhaps when a drug not taken due to overwarning could save a life—there is no conclusive evidence or consensus that they are. Notably, Petitioner's Economists do not even discuss costs related to clutter, presumably because those Type II error costs are not significant.

When the costs of the *relevant* FDA Type II error are considered—and only those costs—the socially optimal standard may be a very stringent labeling standard. It is generally thought that the more information provided to consumers or prescription drugs and their agents (physicians), the more likely it is that decisions made in the marketplace will reflect true economic efficiency—that is, transactions will reflect two parties mutually agreeing to make themselves better off through trade. In the framework developed above, the FDA may optimally choose a P^* that tolerates many Type II errors precisely because the associated Type II error costs are small relative to the costs of Type I errors. Stated differently, what Petitioner's Economists

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[12] The other two alleged Type II error costs—"loss of FDA control over drug labeling" and "problems exacerbated further in state tort cases alleging missing contraindications," Economists' Br. 17, 19—can also be ignored here. Regarding the alleged loss of FDA control, it is not true that state tort liability deprives the medical community of the benefits of FDA expert determinations. And excessive contraindications should be subsumed by the "defensive labeling" category of social costs.

perceive to be an inefficient labeling policy may in fact be the socially optimal policy.

Additionally, failure-to-warn litigation acts in several ways to lessen FDA Type II error in drug approval. Because failure-to-warn litigation incentivizes information disclosure after launch, it is less necessary to have complete information before approval and approval can be more rapid. The safety net offered by failure-to-warn litigation's ability to correct FDA mistakes also enables the FDA to approve promising new products earlier. Further, without the warnings and contraindications incentivized by failure-to-warn litigation, the FDA may decide to withhold approval entirely for some drugs that would otherwise receive warnings on their labels.

5. The FDA Has Taken Active Measures to Counteract Defensive Labeling Relating to State-Level Lawsuits.

Petitioner's Economists implicitly assume that the FDA is insensitive to the potential incentive effects created by state tort liability. In essence, they model the FDA decision-making process as a two-period game in which the FDA determines a labeling standard in period 1 *independent of what takes place in period 2*, and then manufacturers face the prospect of state tort liability in period 2. But any student of game theory recognizes that such behavior is not a stable equilibrium. A more realistic modeling assumption is that the FDA and manufacturers, sophisticated agents, look forward to future possible tort litigation when choosing strategies during the labeling period. See Struve, The FDA and the Tort System: Postmarketing Surveillance, Compensation, and the Role of Litigation, 5 Yale J. Health Pol'y L.

& Ethics 587, 587-88 (2005). Such anticipatory strategies contradict the simplistic modeling assumption used by Petitioner's Economists to describe the FDA's calculus. More importantly, the evidence demonstrates conclusively that the FDA is keenly sensitive to allowing too many Type II errors, especially those potentially caused by state tort liability in the "second period" of a multi-period game.

C. Studies Refute Juries' Alleged Bias in State Tort-Liability Trials.

Finally, empirical evidence refutes Petitioner's Economists assertion that juries in state tort lawsuits inject another systematic bias, skewing the process toward accepting even more Type II errors in the labeling process. The blanket claim that juries behave irrationally when deciding tort lawsuits is made without reference to any rigorous systematic evidence.

A recent review by Dr. Neil Vidmar, professor of psychology and law at Duke University, of empirical analyses of jury decisions in matters requiring expert testimony suggests that juries perform effectively even in cases involving complex circumstances:

> Judge and jury agreement was not significantly different than that found by Kalven and Zeisel almost 50 years before. There was little support for a conclusion that legal complexity or evidentiary complexity accounted for disagreement between judge and jury. More general surveys asking national samples of state and federal judges to evaluate jury performance indicated that the overwhelming majority of judges expressed high agreement with verdicts.

Vidmar, Expert Evidence, the Adversary System, and the Jury, 95 Am. J. Pub. Health S137, S139 (2005). In reviewing another study, Dr. Vidmar avers:

> Taragin et al. obtained access to confidential liability insurer files for lawsuits that occurred in New Jersey between 1977 and 1992. In each case, whenever a medical incident that might constitute malpractice was reported to the insurance company, one or more physicians made an assessment of whether negligence occurred. Among cases that eventually went to trial, physician ratings of whether negligence had occurred were positively related to jury verdicts at a statistically significant level.

Id.

Recent studies also demonstrate that medical malpractice litigation tends to allot compensation when an identifiable medical error was committed and tends not to allot compensation when no medical error was committed. When trained physicians reviewed a random sample of 1,452 medical malpractice cases and produced their own judgments as to medical error, the independent analysts' error findings were overwhelmingly correlated with both the fact of compensation and the amount of compensation.[13] In short, the proposition that juries make irrational decisions when confronted with complex evidence is empirically unwarranted.

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[13] Studdert et al., Claims, Errors, and Compensation Payments in Medical Malpractice Litigation, 354 New Eng. J. Med. 19:2024, 2032 (2006) ("Our findings suggest that moves to curb frivolous litigation, if successful, will have a relatively limited effect on the caseload and costs of litigation. The vast majority of resources go toward resolving and paying claims that involve errors.").

Finally, Petitioner's Economists proposition that the purpose of the state tort suits "is to perform a better balancing act than the FDA," Economists' Br. 19-20, is misguided. State tort lawsuits do not compete with the FDA as the economic goal of both is the maximization of social welfare; rather, these lawsuits serve a complementary function.

CONCLUSION

For these reasons and those more fully developed in respondent's briefing, the Court should affirm the judgment of the Vermont Supreme Court. Congress's refusal to preempt state failure-to-warn litigation is demonstrably wise policy. By reducing information imbalances, incentivizing responsible behavior by drug manufacturers, and ameliorating the effects of Type I and Type II errors in drug approval and labeling, state failure-to-warn litigation complements the FDA regulatory regime and increases social welfare.

Respectfully submitted,

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WYETH,

Petitioner,

v.

DIANA LEVINE,

Respondent.

On Writ of Certiorari to the Supreme Court of Vermont

BRIEF OF THE CENTER FOR STATE ENFORCEMENT OF ANTITRUST AND CONSUMER PROTECTION LAWS, INC. AS *AMICUS CURIAE* IN SUPPORT OF RESPONDENT

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MISCELLANEOUS

Brief of *Amicus Curiae* Constitutional and Administrative Law Scholars in Support of Respondents, *Altria Group, Inc. v. Good*, No. 07-562 23

IN THE

Supreme Court of the United States

No. 06-1249

WYETH,

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Respondent.

On Writ of Certiorari to the Supreme Court of Vermont

BRIEF OF THE CENTER FOR STATE ENFORCEMENT OF ANTITRUST AND CONSUMER PROTECTION LAWS, INC. *AS AMICUS CURIAE* IN SUPPORT OF RESPONDENT

IDENTITY AND INTEREST OF *AMICUS CURIAE*[1]

The Center for State Enforcement of Antitrust and Consumer Protection Laws, Inc. is a nonprofit public interest and research organization. Its mission is to

[1] The parties' letters of consent to the filing of this brief have been filed with the Clerk. No counsel for a party in this case authored this brief in whole or in part, and no person or entity, other than amicus or its counsel, made a monetary contribution to the brief's preparation or submission.

enhance consumer welfare by supporting the fair, effective, and uniform enforcement of antitrust and consumer protection laws at the state level. Among other things, it provides grants to assist in multi-state investigations of price fixing, identity theft and other consumer protection issues; offers educational assistance grants for officials in state attorney general offices; and facilitates access for State Attorneys General to economists with expertise in industrial organization and consumer protection issues.

The Center is concerned that an aggressive program of preemption of state laws by federal regulatory agencies will result in inadequate protection of consumers under state product liability and consumer protection laws. The position of the petitioner and many of its *amici* in this case, including the United States, reflects a broader movement in which federal administrative agencies have joined forces with regulated industries to urge preemption of state tort and consumer protection laws.[2] The Center filed a brief *amicus curiae* in *Watters v. Wachovia Bank, N.A.*, 127 S.Ct. 1559 (2007), addressing the question of what deference courts should afford administrative agencies on questions of preemption.

STATEMENT

Petitioner makes no general claim for deference to agency views about preemption. Likewise, the United States, as *amicus curiae* supporting petitioner, says the Court "need not rely on deference to FDA's views" in order to find preemption (U.S. Brf. at

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[2] *See* Catherine M. Sharkey, *Preemption by Preamble: Federal Agencies and the Federalization of Tort Law*, 56 DEPAUL L. REV. 227 (2007).

26). Nevertheless, the submissions of petitioner and its *amici* rest critically on claims of deference to the views of the Federal Food and Drug Administration (FDA). These claims of deference must be confronted on their own terms. Doing so requires a determination of the proper role of agencies in resolving preemption questions.

Petitioner's first claim is based on the "impossibility" of complying with both federal drug labeling law and Vermont failure-to-warn products liability law. The Vermont Supreme Court rejected this claim, pointing to an FDA regulation (the so-called changes being effected (or CBE) regulation) which plainly permits a pharmaceutical manufacturer to make labeling changes without advance FDA approval, provided those changes "add or strengthen" safety warnings. *See* 21 C.F.R. § 314.70(c)(6)(iii)(A) and (C). In an effort to circumvent the plain meaning of this regulation, petitioner and its *amici* ask the Court to defer to a recent FDA "interpretation" of that regulation which would make it applicable only to changes motivated by new data or studies. Other than some statements made by the FDA in regulatory preambles, however, the only authoritative source for this interpretation is a *proposed* regulation issued by the FDA in January of 2008. *See Supplemental Applications Proposing Labeling Changes for Approved Drugs, Biologics, and Medical Devices*, 73 Fed. Reg. 2848 (2008). In short, the impossibility preemption claim rests on a claim of deference to a recent FDA interpretation that significantly limits the scope of a longstanding FDA regulation, does not have the force of law, and was not promulgated in a process that permits public participation.

Petitioner's second claim is that the application of Vermont failure-to-warn law would frustrate the purposes of the Federal Food Drug and Cosmetic Act (FDCA or Act). State tort liability, however, has long co-existed with federal food and drug regulation. *See Riegel v. Medtronic, Inc.*, 128 S.Ct. 999, 1019 & n.16 (2008) (Ginsburg, J., dissenting) (collecting authorities). The "frustration" identified by petitioner comes about only because of a novel interpretation of the new drug provisions of the Act, namely, that the Act imposes not just a "floor" on information disclosure but also a "ceiling." The source of this floor-and-ceiling interpretation is not any clear language found in the Act itself. Rather, it is an interpretation recently advanced by the FDA, most prominently in a Federal Register notice of 2006. *See Requirements on Content and Format of Labeling for Human Prescription Drugs and Biological Products*, 71 Fed. Reg. 3922, 3933-36 (2006) (hereinafter, "Preemption Preamble"). This theory, again, significantly modifies the longstanding understanding of the Act, does not have the force of law, and was not promulgated in a way that would allow meaningful comment by affected interests.

SUMMARY OF ARGUMENT

The proper role of federal administrative agencies in preemption presents a number of vexing questions, and this Court has understandably been cautious in supplying answers. Three distinct questions can be identified. (1) When can administrative action serve as the basis for a judgment by a court that preemption is required? (2) When can administrative agencies preempt state law on their own authority? (3) What deference or weight should courts give to opinions by administrative agencies about the preemptive effect of federal law? The third question, in

particular, is presented by this case. But the first and second questions are also implicated.

We believe that careful attention to the language and drafting history of the Supremacy Clause, together with considerations of comparative institutional advantage, suggest the following answers. First, agency action can serve as the basis for a judgment of preemption by a court only when the agency acts with the force of law. Agency action that is merely advisory or that does no more than state an agency's legal opinion is not a "Law of the United States," and hence cannot serve as the basis for a judicial finding of preemption. Second, agencies can preempt state law on their own authority only when Congress, acting through the Necessary and Proper Clause, has expressly delegated authority to the agency to preempt, and the agency, in a proper exercise of this authority, has acted with the force of law. Third, unless Congress has expressly delegated authority to preempt, agency statements of opinion about the preemptive effect are entitled to no deference by courts. Courts should look to agencies for guidance on critical issues of legislative fact, most notably the practical impact of diverse state standards on a federal regulatory scheme. When agencies make reasoned determinations of such issues of legislative fact, they are entitled to "weight," especially if the agency has afforded States and other concerned parties a full opportunity to provide input through notice and comment proceedings or otherwise. As to the ultimate legal issue of preemption, however, courts should exercise independent judgment.

As applied to this case, these principles require that the FDA be given no deference on the question

whether the FDCA incorporates a floor or a floor-and-ceiling on the information that drug manufacturers must disclose. Congress has not delegated authority to the FDA to preempt, and the FDA's interpretation has not been adopted in a format that has the force of law. The FDA has offered its opinion that the Act requires preemption of state duty to warn laws. But its reason for preferring a federal monopoly is its own stated belief—undoubtedly shared by every federal agency—that its views are sounder than those of state judges and juries. This argument, however, sheds no light on whether federal standards should be exclusive. Congress could have agreed with the FDA's assessment of its superior competence, and yet still have preferred to perpetuate regulatory competition over appropriate standards, or to preserve state law as a source of compensation for tort victims.

The FDA is also entitled to no deference for its interpretation of the CBE regulation permitting manufacturers to make stronger warnings without advance FDA approval. If the FDA cannot preempt state law directly, it should not be allowed to do so indirectly though the device of "interpreting" a regulation that is otherwise plain on its face.

ARGUMENT

I. THIS COURT HAS CAREFULLY AVOIDED DEFERRING TO ADMINISTRATIVE AGENCIES' VIEWS ON PREEMPTION

Federal administrative action can be relevant to preemption in different ways. It is well established that agency action which has the force of law, such as a legislative regulation, can serve as a source of a

preemption determination *by a court*.[3] There is also little doubt that, in the relatively rare circumstance where Congress has *expressly delegated* authority to an agency to issue preemptive regulations, agencies can preempt state law on their own authority.[4] The principal question here is distinct and is controversial: how much, if any, deference should courts give to statements of agency *opinion* about the preemptive force of federal law? The question has been presented in several recent preemption cases. The Court has, with good reason, carefully avoided any suggestion that agencies are entitled to some general level of deference on preemption questions, whether it be

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[3] *See, e.g.*, *Geier v. Am. Honda Motor Co.*, 529 U.S. 861, 867–68 (2000) (holding that regulation mandating phase-in of passive restraints in automobiles impliedly preempts state tort law claim based on proposition that air bags are mandatory); *CSX Transp., Inc. v. Easterwood*, 507 U.S. 658, 674–75 (1993) (holding that federal regulation governing maximum train speed preempts a negligence claim that a speed under the federal maximum was excessive); *City of New York v. FCC*, 486 U.S. 57, 66–67 (1988) (holding that FCC regulation establishing technical standards to govern the quality of cable television signals preempts more stringent state regulation); *Fid. Fed. Sav. & Loan Ass'n v. de la Cuesta*, 458 U.S. 141, 170 (1982) (holding that Federal Home Loan Bank Board's regulation permitting federally chartered savings and loan associations to exercise due-on-sale clause of mortgages preempts contrary state common law rule).

[4] *See Watters v. Wachovia Bank, N.A.*, 127 S.Ct. 1559, 1583 n.21 (2007) (Stevens, J., dissenting) (collecting statutes). Such authority should not be implied from a general grant of rulemaking authority. *See Gonzales v. Oregon*, 126 S.Ct. 904, 919 (2006) (noting that a delegation of authority to an agency to promulgate "standards" ordinarily does not "include the authority to decide the pre-emptive scope of the federal statute"); Thomas W. Merrill, *Preemption and Institutional Choice*, 102 NW. U. L. REV. 727, 766-69 (2008).

the deference described in *Chevron U.S.A. Inc. v. Natural Resources Defense Council, Inc.*, 467 U.S. 837 (1984), or in *Skidmore v. Swift & Co.*, 323 U.S. 134 (1944).

In *Medtronic, Inc. v. Lohr,* 518 U.S. 470 (1996), the Court considered the effect of an express preemption clause in the Medical Device Amendments to the FDCA. This clause, which applies only to the regulation of medical devices, includes an unusual provision delegating authority to the FDA to "exempt" particular state requirements from preemption. 21 U.S.C. §§ 360k(a), (b) (2000). The Court did not regard this partial delegation of authority to the FDA to mean that courts must defer to any reasonable agency interpretation of the express preemption statute, as would be required by *Chevron*. To the contrary, the Court independently interpreted the ambiguities in the statute, in particular, the uncertainty about the meaning of "requirement." *Medtronic*, 518 U.S. at 486-91. Only after extensive consideration of the interpretative issues did the Court turn to the FDA's views. The Court cited a number of factors that caused it to give those views weight. *Id.* at 496. But the Court did not apply the *Chevron* framework. Instead, it said only that its conclusion was "substantially informed" by the FDA's view about preemption. *Id.* at 495.

The next significant decision to consider agency views on preemption was *Geier v. Am. Honda Motor Co.*, 529 U.S. 861 (2000). The Court held that preemption of state tort liability was required to avoid frustrating a regulation promulgated by the National Highway Traffic Safety Administration calling for a phase-in of passive restraint systems. The Court was careful, however, not to suggest that defer-

ence was required based either on the delegation of power to the agency or the agency's general expertise in matters of auto safety regulation. Instead, the Court concluded only that the agency's views about the impact of state tort law on its regulation were entitled to "some weight" in the circumstances of that controversy. 529 U.S. at 883. The dissenting opinion in *Geier* questioned whether any weight at all should be accorded to the agency's view, given that the States had not been given an opportunity to participate in the development of the agency's opinion. *See id.* at 911-12 (Stevens, J., dissenting).

More recently, in *Watters v. Wachovia Bank, N.A.*, 127 S.Ct. 1559 (2007), the Court reviewed a lower-court judgment that relied on *Chevron* in holding state authority over operating subsidiaries of national banks preempted. The Court affirmed, but the majority found no need to reach the question whether *Chevron* or any other standard of deference was appropriate, since in the majority's view preemption was compelled by the National Banking Act itself. The dissenting opinion did consider what weight should be given to agency views about preemption. *See id.* at 1584 (Stevens, J., joined by Roberts, C.J. and Scalia, J.). The dissenters acknowledged that "expert agency opinions as to which state laws conflict with a federal statute may be entitled to 'some weight,' especially when 'the subject matter is technical' and 'the relevant history and background are complex and extensive.'" *Id.* (quoting *Geier*, 529 U.S. at 883). But the dissenters expressly rejected *Chevron* deference, noting that this would too "easily disrupt the federal-state balance," that agencies are not well designed to represent the interests of States, and that agencies are unlikely to show sufficient respect for state sovereignty. The majority did not

take issue with this analysis, noting only that the question was "academic" given its conclusion that preemption was required by the statute itself. *Id.*

Most recently, the Court again adverted to agency views about preemption in *Riegel v. Medtronic, Inc.*, 128 S.Ct. 999 (2008). As in *Watters*, the Court agreed with the agency that preemption was warranted, but also as in *Watters*, the Court "found it unnecessary to rely upon that agency view" because "the statute itself speaks clearly to the point at issue." *Id.* at 1009. A dissenting opinion briefly discussed the agency's recently-adopted view favoring preemption. *See id.* at 1016 n.8 (Ginsburg, J. dissenting). The dissent noted that this view had been advanced only in an *amicus* brief and, as such, was entitled to "at most" the deference afforded under *Skidmore*. Because the agency had changed its position, the dissent thought that view was entitled to little weight. The majority responded that *if* the agency view were relevant, "mere *Skidmore* deference would seemingly be at issue." *Id.* at 1009. Like the dissent, the majority agreed that, in that hypothetical event, only "reduced" deference would be owed the agency given its change in position. *Id.*

Overall, the Court has approached the question of what, if any, deference is owed to agency views about preemption with appropriate caution. No Justice has endorsed the proposition that agency views about preemption are entitled to *Chevron* deference, even if the preconditions for affording that deference are otherwise satisfied. *See United States v. Mead Corp.*, 533 U.S. 218, 226-27 (2001) (holding that agency views are entitled to *Chevron* deference only if the agency has been delegated authority to act with the force of law and the interpretation has been prom-

ulgated in an exercise of that authority). The discussions of agency views about preemption in the opinions are more consistent with the standard of review prescribed in *Skidmore*. Yet even here, it is noteworthy that no Justice has forthrightly endorsed the application of the *Skidmore* standard in this context.

The best generalization about the state of the law might be that the Court has acknowledged that agencies can lend assistance to courts in resolving preemption questions, primarily by making informed findings of legislative fact about the impact of diverse state requirements on the implementation of a federal regulatory scheme. Taken as a whole, however, the collective pronouncements of the Court do not support affording any deference to agencies on the ultimate legal question whether preemption of state law is warranted. The Court has "assume[d] (without deciding) that [this] question must always be decided *de novo* by the courts." *Smiley v. Citibank (South Dakota), N.A.*, 517 U.S. 735, 744 (1996).

II. THE SUPREMACY CLAUSE CONFERS AUTHORITY ON COURTS, NOT AGENCIES, TO RESOLVE PREEMPTION QUESTIONS

To determine the appropriate role of administrative agencies in resolving questions of preemption it is necessary to begin with the source of authority for federal displacement of state authority. This Court has repeatedly identified the Supremacy Clause as the source of federal authority to preempt state law.[5]

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[5] *See, e.g., Lorillard Tobacco Co. v. Reilly*, 533 U.S. 525, 540–41 (2001) (identifying the Supremacy Clause as the "relatively clear and simple mandate" that allows Congress to "pre-empt[]

The text and drafting history of the Supremacy Clause, in turn, strongly suggest that the judiciary is the institution which is to make such determinations.

A. Preemption Questions Are to Be Resolved by "The Judges in Every State"

As a general matter, the Constitution is addressed to all government actors. Perhaps most notably, the Oath Clause requires that an oath or affirmation supporting the Constitution be administered to all legislative, executive, and judicial officers "both of the United States and of the several States." U.S. Const. art. VI, cl. 3. The Supremacy Clause is at once consistent with this generalization, and yet also includes an exception to it. The Supremacy Clause reads in its totality:

> This Constitution, and the Laws of the United States which shall be made in Pursuance thereof; and all Treaties made, or which shall be made, under the Authority of the United States, shall be the supreme Law of the Land; *and the Judges in every State shall be bound thereby*, any Thing in the Constitution or Laws of any State to the Contrary notwithstanding.

U.S. Const. art. VI, cl. 2. (emphasis added).

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state action in a particular area"); *Nw. Cent. Pipeline Corp. v. State Corp. Comm'n*, 489 U.S. 493, 509 (1989) (referring to Congress's "power under the Supremacy Clause . . . to pre-empt state law"); *de la Cuesta*, 458 U.S. at 152 (declaring that the "pre-emption doctrine . . . has its roots in the Supremacy Clause"); *Morris v. Jones*, 329 U.S. 545, 553 (1947) (stating that when state law "collides with the federal Constitution or an Act of Congress . . . the action of a State under its police power must give way by virtue of the Supremacy Clause").

The first part of the Supremacy Clause, up to the second semi-colon, clearly applies to all government actors. The Constitution, Laws, and Treaties of the United States must be regarded as the "supreme Law of the Land" by all governmental officers, state and federal. After the second semi-colon, however, the Clause is addressed to one branch of government only: the judiciary. The Clause says that "the Judges in every State" shall be bound by authoritative federal law, any provision of state law to the contrary notwithstanding. Note that the Constitution speaks of "the Judges in every State" not merely of "state judges." This was undoubtedly deliberate.[6] As is well known, the Framers left the decision whether to create lower federal courts to future Congresses to make.[7] The phrase, "the Judges in every State" appears to have been drafted to include all judges, state and potentially federal, without regard to where those judges might serve.[8] In other words, the Supremacy Clause specifically singles out the judiciary as an institution, and sets forth a particular rule of decision it is to apply in sorting out competing claims about the application of federal law versus state law.

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[6] For the drafting history of this phrase, *see* FORREST MCDONALD, NOVUS ORDO SECLORUM: THE INTELLECTUAL ORIGINS OF THE CONSTITUTION 255-56 (1985).

[7] *See* 1 MAX FARRAND, THE RECORDS OF THE FEDERAL CONVENTION 104-05, 119, 124-25 (1911).

[8] Several federal courts, including this Court, sit in Washington, D.C. But their judgments arise out of events, and apply to parties, "in every State." The phrase "in every State" should be taken to mean "throughout the United States." Even if the phrase refers only to state court judges, the Supremacy Clause still represents a considered choice by the framers that the judiciary is the appropriate institution to resolve conflicts between federal and state law.

The inference about institutional roles that can be drawn from the text of the Supremacy Clause is powerfully reinforced by evidence of the original understanding of that Clause and its place in the constitutional order. As multiple commentators have carefully documented, the Constitutional Convention had before it three potential mechanisms for assuring that federal law would prevail in the face of opposition grounded in state law: (1) the use of coercive force against defiant states, (2) James Madison's proposal that Congress be given an unrestricted power to "negative" any state law by federal legislation, or (3) the use of the courts to resolve competing claims of federal and state law.[9] Each option corresponded to a particular institutional choice. Force would be deployed by the Executive; the "negative" by the Legislature; court judgments by the Judiciary. The Convention rejected the first two mechanisms in favor of the third or judicial option. The provision that embodied this important decision was the Supremacy Clause.

The choice made by the framers to entrust the resolution of federal-state conflicts to the courts should not be lightly set aside. Of the various institutions familiar to the framers, they concluded that the courts were best situated to mediate between the claims of the national government and the States.

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[9] *See* JACK N. RAKOVE, ORIGINAL MEANINGS: POLITICS AND IDEAS IN THE MAKING OF THE CONSTITUTION 171–72 (1996); Bradford R. Clark, *Separation of Powers as a Safeguard of Federalism*, 79 TEX. L. REV. 1321, 1348–72 (2001); S. Candice Hoke, *Transcending Conventional Supremacy: A Reconstruction of the Supremacy Clause*, 24 CONN. L. REV. 829, 856–75 (1992); James S. Liebman & William F. Ryan, *"Some Effectual Power": The Quantity and Quality of Decisionmaking Required of Article III Courts*, 98 COLUM. L. REV. 696, 709–13 (1998).

Modern administrative agencies were unknown to them, and it is impossible to say what they would have thought of relying on federal agencies to make these decisions. We do know that they were willing to trust the courts to make these decisions. This is not some disembodied "original intent." The choice is fully reflected in the language of the Supremacy Clause, with its specific admonition to "the Judges in every State." That judgment is entitled to the greatest respect.

B. Only Agency Action with the Force of Law Can Preempt

The Supremacy Clause contains within it a second limitation relevant to determining the proper role of agencies in preemption controversies. The Clause makes federal policy dominant only insofar as there is some perceived incompatibility between state law and "[t]his Constitution," "the Laws of the United States which shall be made in Pursuance thereof," or federal treaties made before or after the ratification of the Constitution. Obviously, federal agencies cannot enact constitutional provisions or make treaties. The question, therefore, is whether they can promulgate edicts that qualify under the phrase "Laws of the United States which shall be made in Pursuance [of the Constitution]." The initial impulse is to say "Laws" here must refer to federal statutes—duly enacted and constitutionally valid statutes (those "made in Pursuance of" the Constitution). As one scholar has pointed out, all three forms of federal action singled out as "the supreme Law of the Land" entail a high degree of concurrence by representative institutions. In particular, the concurrence of the Senate (which was thought to represent the interests of the small States) appears to be required for each

form of "supreme" lawmaking.[10] Action by federal administrative agencies would seem not to meet this requirement. This Court has concluded that "[t]he phrase 'Laws of the United States' encompasses both federal statutes themselves and federal regulations that are properly adopted in accordance with statutory authorization."[11] But the reasoning that would support this conclusion has not been spelled out.

The first point to note is that the meaning of the phrase "Laws of the United States" is more uncertain than first appears. The word "Laws" appears twice in the Supremacy Clause, once in the phrase "Laws of the United States" and then again in the admonition that federal supremacy is to be respected by the judges in every state, "any Thing in the Constitution or *Laws* of any State to the Contrary notwithstanding." One could argue that this second reference to "Laws" must also refer to statutes, namely, state statutes. But notice the consequence of this reading: state common law, the most complete body of legal regulation in effect when the Constitution was adopted, might be insulated from preemption under the Supremacy Clause. Thus, if "Laws" in the second appearance of the word were limited to statutes, the effect would be profoundly dysfunctional. To avoid this dysfunction, and the awkwardness of interpreting the same word to mean different things in the same Clause, "Laws of the United States" should also be construed to include more than just legislation enacted by Congress.

Other structural arguments enter into the picture here too. The meaning of "Laws" in the Supremacy

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[10] *See* Clark, *supra*, 79 TEX. L. REV. at 1355–67.

[11] *City of New York*, 486 U.S. at 63.

Clause should be harmonized with the same word in virtually the same phrase in Article III of the Constitution.[12] In that context, it is well established that "Laws of the United States" include not just federal statutes but also decisional rules adopted by courts as a matter of federal law.[13] This suggests that "Laws of the United States" are not limited to federal statutes, but include other rules of decision that have the force and effect of binding federal law, such as federal common law.[14] If federal decisional rules reached by courts can have preemptive effect as "Laws of the United States," it is not clear why rules adopted by federal agencies cannot—in some circumstances at least—be regarded as "Laws of the United States" for Supremacy Clause purposes.

Similarly, consider the appearance of the word "Laws" in the provision of Article II of the Constitution admonishing the President to "take Care that the Laws be faithfully executed." U.S. Const. art. II, § 3. We could again insist that this refers only to statutes enacted by Congress. But surely the Presi-

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[12] U.S. Const. art. III, § 2 ("The judicial Power shall extend to all Cases, in Law and Equity, arising under this Constitution, *the Laws of the United States*, and Treaties made, or which shall be made, under their Authority") (emphasis added). *See* Akhil Reed Amar, *Intratextualism*, 112 HARV. L. REV. 747, 766 (1999).

[13] *See Illinois v. City of Milwaukee*, 406 U.S. 91, 99–100 (1972) (holding that "laws of the United States" for purposes of arising under jurisdiction includes federal common law); *see also Erie R.R. Co. v. Tompkins*, 304 U.S. 64, 78–80 (1938) (holding that "law" as used in Rules of Decision Act includes state common law).

[14] *See City of Milwaukee v. Illinois*, 451 U.S. 304, 312–14 (1981). Federal judicial judgments have been held to be included within the scope of the Supremacy Clause. *Chesapeake & Ohio Ry. Co. v. Martin*, 283 U.S. 209, 220–21 (1931).

dent was also expected to see that judicial judgments are faithfully executed, including those that rest on common law. And it is settled that both subordinate executive branch agencies and the President himself must follow duly promulgated agency regulations unless and until they are rescinded.[15] If agency-made "law" is included in the "Laws" that the President must faithfully execute, why should it not also be included in the "Laws" referenced in the Supremacy Clause?

To be sure, the word "Laws" cannot be stretched beyond all recognition. Laws must refer, at a minimum, to explicit or implicit rules that bind the future exercise of governmental authority. Thus, for example, a sense of the Senate resolution or a dictum in an opinion of a court should not be regarded as "Laws" for Supremacy Clause purposes. In the agency context, only agency action that has the force of law should be regarded as providing a predicate for preemption. Legislative regulations and self-executing agency orders have this quality; policy statements and interpretative regulations do not.

It is also necessary to demonstrate that agency action has been adopted "in Pursuance of" the Constitution. Here, the Necessary and Proper Clause provides appropriate guidance. *See* U.S. Const. art I, § 8, cl. 17. If Congress has delegated authority to an agency to act with the force of law, and an agency has fulfilled the conditions for exercising that delegated power, then it is possible to speak of the resulting directive as being one that has been made "in Pursuance of" the Constitution, to wit, in pursuance

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[15] *See United States v. Nixon*, 418 U.S. 683, 696 (1974).

of a legislative delegation of lawmaking authority permitted by the Necessary and Proper Clause.

Together, these considerations carry with them a significant limitation on the *type* of agency pronouncement that can qualify as a source of preemption. Of the various types of action agencies can take, only agency action based on a delegation of authority from Congress and having the force of law can qualify as a source of preemption consistent with the language of the Supremacy Clause. Legislative regulations satisfy both conditions implied by the Clause for identifying the type of agency action that can serve as a source of preemption. Such regulations take the form and effect of a statute, and they are issued pursuant to a delegation of authority from Congress to act with the force of law.[16] Agency orders issued pursuant to an adjudication that have self-executing legal force also qualify as having the force of law. Other types of agency action, such as policy statements, interpretative rules, opinion letters, and discussions in preambles, fail to meet either or both of the conditions imposed by the Clause.

Limiting agency action that can serve as the source of preemption to that which has the force of law has other positive consequences. Under the Administrative Procedure Act (APA), the issuance of legislative regulations generally requires that the agency

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[16] *See, e.g.*, *Am. Postal Workers Union, AFL-CIO v. U.S. Postal Serv.*, 707 F.2d 548, 558 (D.C. Cir. 1983) ("A rule can be legislative only if Congress has delegated legislative power to the agency and if the agency intended to use that power in promulgating the rule at issue."). *See Mead*, 533 U.S. at 226–27; *see also Gonzales v. Oregon*, 546 U.S. at 255–56; *Nat'l Cable & Telecomm. Ass'n v. Brand X Internet Servs.*, 545 U.S. 967, 980–81 (2005).

comply with notice and comment procedures.[17] This creates an opportunity for States and other interested parties to express their views before potentially preemptive regulations are adopted. Similarly, agency adjudications that lead to binding orders are subject to significant hearing requirements, either under the APA or due process decisional law.[18] In addition, agency action having the force of law, with rare exceptions, is subject to judicial review, which helps insure that agencies act within the bounds of their legal authority. Limiting the sources of agency preemption to action with the force of law thus helps to insure that those entities most affected by a decision to displace state law have a voice in the matter.

Modern administrative law norms also require that agencies disclose relevant data and provide a reasoned response to material objections raised in the rulemaking process.[19] These disclosure and reason-giving requirements can help supply information that bears on the choice between uniform federal rules or diverse state rules. Accordingly, limiting agency action that can be the source of preemption to legislative rules would also help generate more information and analysis that bears on the pragmatic issues implicated in any decision to displace state law.

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[17] 5 U.S.C. §§ 553(b), (c) (2000); *cf.* 5 U.S.C. § 553(a)(2) (2000); *Mead*, 533 U.S. at 244 (Scalia, J., dissenting).

[18] *See* 5 U.S.C. §§ 556, 557 (2000); *Mathews v. Eldridge*, 424 U.S. 319 (1976).

[19] *See, e.g.*, *Motor Vehicle Mfrs. Ass'n v. State Farm Mut. Auto. Ins. Co.*, 463 U.S. 29, 42–44 (1983).

III. CONSIDERATIONS OF COMPARATIVE ADVANTAGE REINFORCE THE CONCLUSION THAT THE JUDICIARY IS THE PROPER INSTITUTION FOR RESOLVING PREEMPTION QUESTIONS

The judiciary is also the preferred institution for resolving questions of preemption when broader considerations of comparative institutional advantage are taken into account.

A. Preemption Entails the Application of Law Developed by Courts

Given its origins in the Supremacy Clause, it is not surprising that the legal doctrine governing the decision to displace state law through preemption has been developed exclusively by courts, and in particular by this Court. This carefully evolved doctrine is trans-substantive, in the sense that it applies across all fields of regulation. Administrative agencies have played no role in the development of preemption doctrine. When agencies have offered their views about the desirability or need for preemption, they have typically framed their analysis in terms of the categories and precedents developed by the courts.[20] In other words, agencies have justified their support (or opposition) to preemption largely in terms of their reading of judicial opinions, a source of authority that agencies have no special insights in interpreting, and which the judiciary is presumably in a better position to explicate.

In addition, the decision to displace state law presents a variety of concerns that point toward the need

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[20] *See* Nina A. Mendelson, Chevron *and Preemption*, 102 MICH. L. REV. 737, 784-86 (2004).

for a general jurisprudence of preemption which can be developed and applied in a uniform fashion.[21] Only the courts, and in particular this Court—which has the ability to review questions of preemption that arise both from federal and state courts—can serve the function of reviewing preemption questions in a manner that maintains a unified jurisprudence of preemption sensitive to the many systemic values at stake.

B. Preemption Implicates Considerations of Federalism

The decision to displace state law through preemption also implicates important questions of federalism. *See, e.g.*, *Medtronic*, 518 U.S. at 488 (describing preemption of state common law remedies as a "serious intrusion into state sovereignty"). Indeed, from the perspective of the States, there is little difference between a judgment that state law is unconstitutional, and a judgment that state law is preempted. Both types of judgments nullify otherwise duly enacted state statutes and common law rules of decision. In so doing, both types of judgments subtract from the power the States otherwise enjoy as sovereign entities.[22]

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[21] *See* Merrill, *supra*, NW. U. L. REV. at 947-51.

[22] To be sure, preemption decisions can be overridden by Congress. But mobilizing Congress to overrule preemption decisions is difficult, and has rarely been successful. *See* Note, *New Evidence on the Presumption Against Preemption: An Empirical Study of Congressional Responses to Supreme Court Preemption Decisions*, 120 HARV. L. REV. 1604, 1613-14 (2007). Moreover, some constitutional judgments—those based on the dormant aspect of the Commerce Clause—are also subject to revision by Congress, further revealing the close connection between preemption and constitutional invalidation.

Part of our received tradition is the understanding that the judiciary has unique competence to resolve questions of constitutional federalism. Thus, for example, this Court has declined to adopt interpretations of statutes that raise questions of constitutional federalism that otherwise can be avoided, *see, e.g.*, *Gregory v. Ashcroft*, 501 U.S. 452 (1991), and has declined to defer to agency decisions that raise questions of constitutional federalism that can be avoided. *See, e.g., Gonzales v. Oregon*, 126 S.Ct. at 925; *Solid Waste Agency of Northern Cook County v. United States Army Corps of Engineers*, 531 U.S. 159, 172-73 (2000). The decision to displace state law through preemption should be informed by an understanding of which areas of regulation have been delegated to the federal government, which have traditionally been committed to the States, and when constitutional sensitivities would be irritated either by a determination of concurrent authority or of exclusive federal competence.[23] Agencies are specialized institutions, intensely focused on the details of the particular statutory regimes they are charged with administering. By design and tradition, they are not expected to ponder larger structural issues such as the relative balance of authority between the federal and state governments, the importance of preserving state autonomy, the value of allowing policy to vary in accordance with local conditions, or the systemic advantages of permitting state experimentation with divergent approaches to social problems. *See Gregory v. Ashcroft*, 501 U.S. at 458-59 (summarizing the systemic benefits of federalism).

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[23] *See generally* Brief of *Amicus Curiae* Constitutional and Administrative Law Scholars in Support of Respondents, *Altria Group, Inc. v. Good*, No. 07-562.

C. Preemption Implicates the Scope of Agency Power

Determining whether federal law ousts state law also implicates the scope of agency authority. *See Louisiana Public Service Comm'n v. FCC*, 476 U.S. 355, 374-75 (1986) ("An agency may not confer power upon itself. To permit an agency to expand its power in the face of a congressional limitation on its jurisdiction would be to grant to the agency the power to override Congress. This we are both unwilling and unable to do."). There are a variety of reasons why agencies are not the best monitors of the scope of their own authority. Agencies may at times engage in empire-building, or may resent implicit competition from other sources of regulatory authority like States. Analysts have long observed that agencies, particularly ones devoted to regulation of a single industry, can become too closely identified with the interests of the industry they are supposed to regulate.[24]

Congress has provided for judicial review of agency action in significant part to assure that agencies stay within the bounds of their delegated authority. This Court has been reluctant to carve out any general exception from *Chevron* for agency interpretations that transgress the bounds of agency authority, presumably because of the difficulty of distinguishing

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[24] *See, e.g.*, MARVER H. BERNSTEIN, REGULATING BUSINESS BY INDEPENDENT COMMISSION (1955); George J. Stigler, *The Theory of Economic Regulation*, 2 BELL J. ECON. & MGMT SCI. 3 (1971); Samuel P. Huntington, *The Marasmus of the ICC: The Commission, the Railroads, and the Public Interest*, 62 YALE L.J. 171 (1953); *see generally* Steven P. Croley, *Theories of Regulation: Incorporating the Administrative Process*, 98 COLUM. L REV. 1 (1998) (providing an overview of theories and empirical studies).

between "jurisdictional" and "non-jurisdictional" decisions. *Compare Mississippi Power & Light Co.* v. *Mississippi ex rel. Moore*, 487 U.S. 354, 381 (1988) (Scalia, J., concurring in judgment) *with id.* at 386-87 (Brennan, J., dissenting). There is no need in this case, however, to tackle this more general problem. Questions about whether state law should be preempted by federal law are not handicapped by any definitional conundrum similar to the one presented by determining when an agency has acted outside its "jurisdiction." The question whether federal law preempts state law is discrete and readily differentiated from other issues of interpretation. *See* Mendelson, *supra*, 102 MICH. L. REV. at 796 ("Preemption questions are relatively easy to distinguish, *ex ante*, from other categories of interpretative questions, so withdrawing deference on preemption issues would not introduce significant new uncertainty-based costs. . . ."). Consequently, the decision to preempt can be subject to independent judicial review, allowing courts to police the boundaries of agency authority—along this dimension at least—without calling into question the general principle of deference established by *Chevron*.

IV. THE FDA'S VIEWS ON PREEMPTION DO NOT WARRANT DEFERENCE IN THIS CASE

In light of the foregoing considerations, we may summarize the permissible role of administrative agencies in preemption controversies in the form of three principles. (1) Administration action can serve as the basis for a determination of preemption *by a court* only if the administrative action has the force of law, specifically, only if that action takes the form of a binding legislative regulation or a self-executing

adjudicatory order. (2) Administrative agencies can preempt state law on their own authority (and their opinions about the preemptive effect of agency action are entitled to strong deference) only if the power to preempt has been *expressly delegated* to the agency by Congress. (3) Statements of opinion by administrative agencies about the preemptive effect of federal law (assuming the power to preempt has not been expressly delegated to the agency by Congress) are not entitled to judicial deference, although courts can draw upon the assistance of agencies in resolving questions of legislative fact that bear on matters of preemption. Under the foregoing principles, the FDA's views about the preemptive force of the Food Drug and Cosmetic Act in this case are entitled to no deference and should be given minimal weight.

A. The FDA's "Floor and Ceiling" Interpretation of the Act is Entitled to No Deference

A potentially critical issue in this case is whether the FDCA imposes only a floor on information disclosure about FDA-approved drugs, or both a floor and a ceiling. The FDA has advanced the floor-and-ceiling interpretation in its Preemption Preamble, and the Solicitor General, on behalf of the United States, has filed a brief endorsing this interpretation. The FDA's interpretation cannot itself serve as a basis for preemption, and is entitled to no deference.

The FDA's floor-and-ceiling interpretation has never been adopted by the agency in a form that has the force of law, and hence cannot itself serve as a basis for a finding of preemption. The floor-and-ceiling interpretation evidently originated in *amicus curiae* briefs filed by the Justice Department on behalf of

the FDA in products liability cases. *See* 71 Fed. Reg. at 3934. In the Preemption Preamble, the FDA sought to "set forth in some detail the arguments made in those amicus briefs." *Id.* However, no attempt was made to codify the floor-and-ceiling interpretation in the Code of Federal Regulations, as would be appropriate if it had the force of law. *See American Mining Congress v. Mine Safety & Health Admin.*, 995 F.2d 1106, 1109 (D.C. Cir. 1993). And the FDA has not claimed, nor could it, that the floor-and-ceiling interpretation was a necessary step it had to reach in order to issue the revised Labeling Rules, to which they were attached. *Cf. National R.R. Passenger Corp. v. Boston & Maine Corp.*, 503 U.S. 407, 420 (1992) (agency interpretation entitled to deference if it is a "necessary presupposition" of the decision reached). At most, the floor-and-ceiling interpretation reflects the FDA's legal opinion about the proper conclusion a court should reach about the preemptive effect of its labeling regulations. It was simply that—an agency legal opinion—not agency action having the force of law.

Similarly, no argument has been or could be made that Congress has delegated authority to the FDA to preempt state regulation of drug labeling or state tort law dealing with failure to warn about pharmaceutical hazards. Congress knows how to delegate such authority, as when it delegated authority to the FDA to adjust the scope of preemption related to medical devices. *See* 21 U.S.C. §§ 360k(a), (b) (2000); *Medtronic*, *supra*. The claim of preemption in this case is based solely on implied preemption doctrines, not on delegated authority. It follows that no deference is due to the FDA's opinions about the need for preemption.

Moreover, insofar as the FDA's new theory rests on determinations of legislative fact, it is entitled to little or no weight. This Court has stated that even if administrative views on preemption do not compel deference, they may be entitled to "weight," especially if they illuminate the critical question of how diverse state requirements or standards would affect the federal regulatory regime. *See* Part I, *supra*. The FDA has said virtually nothing about this critical issue, however, and hence its analysis is not entitled to any "weight." Most of the agency's arguments have either been conceptual in nature, or have stressed empirical propositions that are irrelevant to the need for a single federal disclosure standard, as opposed to multiple standards.

The agency's most complete defense of the floor-and-ceiling construction of the Act is set forth in its Preemption Preamble. *See* 71 Fed. Reg. at 3935. The agency's arguments in support of this construction, however, largely reduce to the proposition that the FDA believes it is a better regulator than state courts and juries. Thus, the FDA argued that "[o]verwarning, just like underwarning, can similarly have a negative effect on patient safety and public health," *id.*, and that the FDA has greater expertise than "lay judges and juries." *Id.* Whether or not these claims are correct, they do not illuminate the critical question of whether the very existence of diverse standards would undermine or compromise the federal scheme. Even if Congress agreed with the FDA's assessment of its superior expertise, it does not follow that Congress would want to eliminate all competition among political jurisdictions over disclosure standards, or that it would want to eliminate the traditional source of compensation for persons injured by inadequate warnings. Similarly, the Solicitor

General's brief filed in this Court, while purporting to "articulate[] a more generally applicable rule of decision" than the FDA provided in its Preamble (U.S. Brf. at 27), offers no substantive argument or evidence that would explain why a single federal labeling standard is necessary, or how the existence of multiple labeling standards would frustrate or undermine the federal regulatory scheme.

Moreover, the agency has never solicited public comment on the important factual premises that might support a preemption finding. The lengthy Notice of Proposed Rulemaking (NOPR) that initiated the process of public comment on the revised Labeling Rules provided no clue that the FDA was considering action that would have any preemptive effect. *See Requirements on Content and Format of Labeling for Human Prescription Drugs and Biologics; Requirements for Prescription Drug Product Labels*, 65 Fed. Reg. 81082-81124 (2000); *see also* 66 Fed. Reg. 17375 (2001) (extending comment period). Indeed, the NOPR said the "proposed rule does not preempt State law." 65 Fed. Reg. at 81103. Thus, the FDA never put the States and other interested parties on notice that it might endorse a legal theory that would strip the States of significant regulatory authority. Commentators have uniformly agreed that agencies need to provide better notice and hearing opportunities if their findings about the need for federal uniformity are to be taken seriously.[25]

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[25] *See, e.g.*, Mendelson, *supra*, 102 MICH. L. REV. at 777-78; Merrill, *supra*, 102 NW. U. L. REV. at 756-57; 764-65; Sharkey, *supra*, 56 DEPAUL L. REV. at 252-54.

B. The FDA Is Not Entitled to *Auer* Deference for Its Interpretation of the CBE Regulation

The FDA should also be denied any deference under *Auer v. Robbins*, 519 U.S. 452 (1997), for its recent "interpretation" of the CBE regulation that would limit pre-approval changes in drug label warnings to those supported by new data or studies. Preliminarily, we would note that the issue with respect to impossibility is very narrow. Under the Vermont Supreme Court's reading of the CBE regulation, which is consistent with its plain language, a drug manufacturer may change its labeling to strengthen warnings of a specific safety hazard before it obtains FDA approval of the change. Under petitioner's and the FDA's view of the matter, unless the manufacturer can point to new studies or data supporting a strengthened warning, the manufacturer must seek and obtain the FDA's approval before making any change. If the FDA eventually *agrees* with the proposed change, then of course there would be no conflict between federal and state law, and the change could be implemented. So the question boils down to what happens in the interim period between the announcement of a new, strengthened warning requirement as a matter of state law, and the FDA's review of a manufacturer's proposal as to how to comply with that requirement. Can the label be changed until the FDA disapproves it, or does the new label remain in limbo until the FDA approves it?

The question is not only narrow, it may be of only transitory significance. The FDA has published a Notice of Proposed Rulemaking seeking comment on whether it should codify its new restrictive interpretation of the CBE regulation, limiting a manu-

facturer's ability to strengthen label warnings to situations where new data or studies support the heightened warning. *See Supplemental Applications Proposing Labeling Changes for Approved Drugs, Biologics, and Medical Devices*, 73 Fed. Reg. 2848 (2008). If the FDA ultimately decides to promulgate such a regulation, and if this revision is determined to be consistent with the Act and relevant procedural requirements, then the FDA's interpretation could be considered by a court in determining its implications for preemption. As things now stand, however, the rule is only a proposal; it has no legal effect.

All of which highlights why it is inappropriate to defer to the FDA's "interpretation" of the CBE regulation in this case, which would achieve the same result as the proposed regulation but by the shortcut of acting in a fashion that lacks the force of law. For the reasons previously given, agency action can provide the basis for a preemption determination by a court only when the agency acts with the force of law. The FDA (we assume) acted with the force of law when it adopted the CBE regulation. But it has not acted with the force of law in amending that regulation to incorporate the new-data-or-studies limitation—at least not yet. Consequently, to grant *Auer* deference to the FDA's "interpretation" of the CBE regulation as incorporating the new limitation would sanction an end-run around the principle that agency action has potential preemptive force only when it has the force of law.

Similarly, for reasons previously given, courts should give agencies strong deference on questions of preemption only when Congress has *expressly delegated* authority to the agency to preempt state law. Congress has not delegated such authority to

the FDA. Consequently it would be inappropriate to grant *Chevron* or similar strong deference to an FDA determination that the Act preempts state warning requirements pending FDA approval. If an FDA interpretation of the Act as requiring preemption would not garner strong deference, it would be improper to give a similar degree of strong deference to an FDA "interpretation" of a regulation that would yield the same result. This would allow agencies to bootstrap their way to deference by issuing vague regulations, which are then "clarified" by interpretations that would be given strong deference. *See Thomas Jefferson Univ. v. Shalala*, 512 U.S. 504, 525 (1994) (Thomas, J., dissenting).

This Court has previously recognized that *Auer* deference should not be used to achieve by indirection results that would not be permitted if pursued by an agency directly. In *Gonzales v. Oregon*, the Court ruled that *Auer* cannot be applied to a regulation that merely "parrots" the language of the statute. 126 S.Ct. at 915-16. The reason is straightforward. If an agency would not be entitled to *Chevron* deference for an interpretation of a statute (because the matter is beyond the scope of the agency's delegated authority), then the agency cannot achieve the same end by issuing a regulation that tracks the statute and then purporting to "interpret" the regulation. For the same fundamental reason, if an agency has not acted in a manner that would justify preemption, and would not be entitled to deference on a question of preemption, it should not be allowed to achieve this impermissible result through the device of an interpretation of a regulation.

CONCLUSION

For the foregoing reasons, the judgment of the Vermont Supreme Court should be affirmed.

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WYETH,

Petitioner,

v.

DIANA LEVINE,

Respondent.

On Writ of Certiorari to the Supreme Court of Vermont

BRIEF OF THE CHAMBER OF COMMERCE OF THE UNITED STATES OF AMERICA AS *AMICUS CURIAE* IN SUPPORT OF PETITIONER

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BRIEF OF THE CHAMBER OF COMMERCE OF THE UNITED STATES OF AMERICA AS *AMICUS CURIAE* IN SUPPORT OF PETITIONER

INTEREST OF THE *AMICUS CURIAE*[1]

The Chamber of Commerce of the United States of America (the Chamber) is the world's largest business federation. The Chamber represents an underlying membership of more than three million companies and professional organizations of every size, in every industry sector, and from every region of the country. An important function of the Chamber is to represent the interests of its members in matters before Congress, the Executive Branch, and the courts. To that end, the Chamber regularly files *amicus curiae* briefs in cases that raise issues of vital concern to the Nation's business community.

This is such a case. The Chamber's members include not only pharmaceutical companies, which depend on the doctrine of implied preemption as protection against state and local mandates that conflict with labeling requirements imposed by federal law, but also millions of other businesses that are subject to preemptive federal statutes and regulations. The Supremacy Clause of the Constitution, which is the fountainhead of the doctrine of implied conflict preemption, serves a

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[1] The parties' letters of consent to the filing of this brief have been filed with the Clerk. Under Rule 37.6 of the Rules of this Court, *amicus curiae* states that no counsel for a party has authored this brief in whole or in part, and no counsel or party made a monetary contribution intended to fund the preparation or submission of this brief. No person or entity, other than the *amicus curiae*, its members, or its counsel, has made a monetary contribution to this brief's preparation or submission.

vital structural role in our Nation's government by protecting federal law and programs against encroachment and interference by subordinate governments. It also helps to create unified and rational markets for nationally distributed goods and services by ensuring that uniform federal regulation is not undermined or subverted by state and local law, including state tort law as applied by lay juries. Accordingly, the Chamber and its members have a substantial interest in ensuring that this Court properly resolves the important issues raised in this case.

STATEMENT

1. The Supremacy Clause of the Constitution provides: "This Constitution, and the laws of the United States . . . and all Treaties . . . shall be the supreme Law of the Land; and the Judges in every State shall be bound thereby; any Thing in the Constitution or Laws of any State to the Contrary notwithstanding." U.S. CONST. art. VI, cl. 2. State and local laws that conflict with federal law are preempted "by direct operation of the Supremacy Clause." *Brown* v. *Hotel & Restaurant Employees & Bartenders Int'l Union Local 54*, 468 U.S. 491, 501 (1984).

This Court's decisions interpreting the Supremacy Clause – and articulating what has come to be known as the doctrine of implied conflict preemption – stretch back to the earliest days of the Republic. See, *e.g.*, *Gibbons* v. *Ogden*, 22 U.S. (9 Wheat.) 1 (1824); *Houston* v. *Moore*, 18 U.S. (5 Wheat.) 1 (1820); *M'Culloch* v. *Maryland*, 17 U.S. (4 Wheat.) 316 (1819). "[S]ince our decision in *M'Culloch*," the Court has explained, "it has been settled that state law that conflicts with federal law is 'without effect.'" *Cipollone* v. *Liggett Group, Inc.*, 505 U.S. 504, 516 (1992).

The Court's precedents have separately discussed "'conflicts' that prevent or frustrate the accomplishment of a federal objective" (so-called "obstacle" preemption) and "'conflicts' that make it 'impossible' for private parties to comply with both state and federal law" ("impossibility" preemption). *Geier* v. *American Honda Motor Co.*, 529 U.S. 861, 873-74 (2000). In *Geier*, this Court recently refused to "drive[] a legal wedge" between the doctrines of obstacle and impossibility preemption, reaffirming its longstanding understanding that "both forms of conflicting state law are 'nullified' by the Supremacy Clause." 529 U.S. at 873-74; *id.* at 874 ("We see no grounds . . . for attempting to distinguish among types of federal-state conflict for purposes of analyzing whether such a conflict warrants pre-emption in a particular case.").

This Court's *test* for obstacle preemption has been the same for more than 65 years, and is derived from *Hines* v. *Davidowitz*, 312 U.S. 52, 67 (1941): The Supremacy Clause nullifies state or local law that "stands as an obstacle to the accomplishment and execution of the full purposes and objectives of Congress." See also *Perez* v. *Campbell*, 402 U.S. 637, 649-50 (1971) ("Since *Hines* the Court has frequently adhered to this articulation of the meaning of the Supremacy Clause.") (citing multiple cases). But the *doctrine* of obstacle preemption is much older than *Hines*, and indeed goes back to this Court's earliest preemption decisions. See *Perez*, 402 U.S. at 649 (obstacle preemption has roots extending at least back to *Gibbons* v. *Ogden*, which recognized that state laws that "'*interfere with*, or are contrary to the laws of Congress . . . ,' are invalid under the Supremacy

Clause") (quoting 22 U.S. (9 Wheat.) at 211) (emphasis added).[2]

Obstacle preemption can occur not only where the goals of state and federal law are incompatible, but also where state law "interferes with the *methods* by which the federal statute was designed to reach [its] goal." *International Paper Co.* v. *Ouellette*, 479 U.S. 481, 494 (1987) (emphasis added). Thus, as with other forms of implied conflict preemption, "[t]he fact of a common end hardly neutralizes conflicting means." *Crosby* v. *National Foreign Trade Council*, 530 U.S. 363, 379 (2000).

2. This case arises out of a medical incident in which a physician assistant inadvertently injected Phenergan, an anti-nausea drug manufactured by petitioner Wyeth, into an artery (rather than as intended, into a vein) in the arm of respondent Diana Levine. In four separate places, Phenergan's two-page label warned of the risk of gangrene arising from arterial exposure. For example, the "Warnings" section cautioned that "extreme care should be exercised to avoid . . . inadvertent intra-arterial injection" because its "likely" consequences would be "pain" and "gangrene requiring amputation." JA 390. Although Phenergan's

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[2] See also *Houston*, 18 U.S. (5 Wheat.) at 22-24 (Supremacy Clause overrides state laws whenever their enforcement would "thwart[]" or "oppose[]" the "will of Congress," even if they do not contradict federal law); *M'Culloch*, 17 U.S. (4 Wheat.) at 427 ("It is of the very essence of [federal] supremacy, to remove all *obstacles* to its action within its own sphere, and so to modify every power vested in subordinate [state] governments, as to exempt its own operations from their . . . influence.") (Marshall, C.J.) (emphasis added); *Savage* v. *Jones*, 225 U.S. 501, 533 (1912) (a "state law must yield" if it prevents "the purpose of" a federal law from being accomplished or "frustrate[s]" the federal law's "operation").

labeling specified a maximum dosage of 25 mg for nausea and instructed that intravenous (IV) injection should be "stopped immediately" if the patient complains of pain, JA 390-91, the physician assistant gave respondent a 50 mg dose – twice the maximum – and administered it without pausing in spite of respondent's complaints of pain. JA 105, 110-11, 183.

After settling a medical malpractice suit, respondent filed this product liability action against Wyeth in the Vermont courts. Respondent's theory of liability was that Phenergan was "not reasonably safe for intravenous administration" through a method known as "IV push" – in which a syringe pushes the medication directly into the patient's vein (or into the flexible tubing of an infusion set already inserted in the vein), as opposed to "IV drip," in which the medication is added to a hanging IV bag of saline solution – because the risks of IV push administration outweighed its "therapeutic benefits." Accordingly, respondent claimed, Wyeth should have included a categorical statement in the drug's labeling to the effect that the drug should *not* be used intravenously (at least not through the IV push method). A Vermont jury awarded respondent approximately $7 million in damages.

The Food and Drug Administration (FDA) approved Phenergan for marketing in 1955.[3] Phenergan's labeling lists both IV and intramuscular (IM) injection as approved methods of administration.

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[3] As petitioner's brief demonstrates (at 11-16), in the 45 years between that approval decision and the medical incident involving respondent, the FDA extensively regulated Phenergan's labeling – including, specifically, both the label's statements concerning the risks attendant to inadvertent intra-arterial injections and its instructions about how to minimize the risk of intra-arterial injections.

JA 390. The FDA's approval of both methods reflects the agency's expert judgment, based on its evaluation of scientific data, that both methods are safe and effective. As Phenergan's labeling notes, IV administration produces clinical effects four times faster than IM administration, and thus is beneficial for certain patients, including those in need of rapid relief. JA 390. Earlier on the day of the medical incident, respondent had received an IM injection of Phenergan, but had returned to the health clinic because that injection had not provided her with relief. JA 19; Pet. App. 2a.

In affirming, a divided Supreme Court of Vermont rejected Wyeth's arguments that respondent's claims were impliedly preempted. Pet. App. 1a-48a. Wyeth argued that respondent's claims both rested on duties that it was impossible for Wyeth to honor without violating federal law, and also frustrated the purposes of the Food, Drug, and Cosmetic Act (FDCA) labeling requirements as implemented by the FDA. The majority acknowledged that (1) "FDA regulations mandate the general format and content of all sections of labels . . . as well as the risk information each section must contain"; (2) the FDA's approval of a new drug application is "conditioned upon the applicant incorporating the specified labeling changes exactly as directed"; and (3) "[o]nce a drug and its label have been approved, any changes to the label ordinarily require submission and FDA approval." Pet. App. 9a (internal quotation marks omitted). Nevertheless, "[w]hile specific federal labeling requirements and state common-law duties might otherwise leave drug manufacturers with conflicting obligations," the court reasoned, a "key FDA regulation" – 21 C.F.R. § 314.70 – "allows, and arguably encourages, manufacturers to add and strengthen warnings that, despite FDA

approval, are insufficient to protect consumers." Pet. App. 10a-11a. Relying on that reading of Section 314.70, which is commonly known as the "Changes Being Effected" (or "CBE") regulation, the Vermont Supreme Court rejected Wyeth's argument of impossibility preemption. Pet. App. 16a-19a.

The lower court also rejected Wyeth's argument based on obstacle preemption. Pet. App. 19a-24a. In so doing, it relied largely (*id.* at 21a-23a) on a provision added to the FDCA in 1962, which states: "Nothing in the amendments made by this Act to the [FDCA] shall be construed as invalidating any provision of State law . . . unless there is a *direct and positive* conflict between such amendments and such provision of State law." Drug Amendments of 1962, Pub. L. No. 87-781, § 202, 76 Stat. 780, 793 (1962) ("Section 202") (emphasis added). In the majority's view, the highlighted language reflects an intent on Congress's part to bar the operation of "obstacle" preemption with respect to the FDCA while preserving the operation of "impossibility" preemption. Pet. App. 21a-23a.

Thus, the Vermont Supreme Court's rejection of Wyeth's arguments for obstacle and impossibility preemption rested on the court's reading of a particular federal statute and regulation. But the court's interpretation was also based on secondary rules about how the preemption analysis should be conducted. Specifically, in rejecting both of Wyeth's implied preemption arguments, the Vermont Supreme Court invoked "the presumption against preemption." Pet. App. 14a, 23a. And the court (again relying on its reading of Section 202) declined to give any weight to certain statements made by the FDA relating to preemption and the adverse and disruptive effects of certain state-law product liability lawsuits on the federal regulatory

scheme, thereby avoiding a "difficult question of administrative law" concerning the degree of deference properly owed to the FDA's statements. Pet. App. 25a-28a.

INTRODUCTION AND SUMMARY OF ARGUMENT

This case presents important issues of preemption law that arise in the distinctive setting of the federal government's longstanding oversight and regulation of prescription drugs pursuant to the Food, Drug, and Cosmetic Act, 21 U.S.C. §§ 301 *et seq.* The Supreme Court of Vermont ruled that respondent's state-law tort claims do not offend the Supremacy Clause even though they would require Wyeth to alter Phenergan's FDA-approved labeling by adding a statement that IV push administration – a use that the FDA in its expert judgment has determined is safe and effective – should not be employed because its risks outweigh its benefits. That ruling was mistaken. Respondent's claims are a direct challenge to the FDA's labeling judgments, based on state-law duties that are squarely at odds with the requirements of federal law. Respondent's claims are barred by both impossibility and obstacle preemption.

I. The Chamber files this brief in part to address a broader concern that the Vermont Supreme Court's decision reflects a misunderstanding of the vital importance – and deep historical roots – of the doctrine of implied conflict preemption in our constitutional scheme. As this Court has repeatedly recognized, that doctrine flows directly from the Supremacy Clause itself. And both variants of implied conflict preemption that are at issue in this case – impossibility and obstacle preemption – have deep roots in this Court's decisions. This Court has refused to "drive[] a legal wedge" between obstacle and impossibility preemption

and has made clear that there are "no grounds . . . for attempting to distinguish among types of federal-state conflict for purposes of analyzing whether such a conflict warrants pre-emption in a particular case." *Geier* v. *American Honda Motor Co.*, 529 U.S. 861, 873-74 (2000). And with good reason: obstacle and impossibility preemption serve equally crucial roles in protecting *all* of federal law and *all* federal regulatory programs from interference by state and local governments.

The lower court's decision appears to reflect a misguided assumption that obstacle preemption is somehow less important or entitled to less respect under the Supremacy Clause. But as the origins of the Supremacy Clause in the Constitutional Convention make clear, the Framers chose to assign responsibility for ensuring the supremacy of federal law to the judicial branch in the first instance. Obstacle preemption is part of that assignment, as this Court's earliest preemption cases recognize. Moreover, recent scholarship has established that the Supremacy Clause is in the form of a "*non obstante*" clause – a directive specifically aimed at judges and instructing them not to read federal laws narrowly to avoid conflicts with state laws under the Supremacy Clause. Concerns expressed by some judges and commentators that obstacle preemption is unduly subjective or discretionary overlook these facts. In addition, the inquiry into obstacle preemption is no more subjective than many other legal issues that judges are routinely called on to decide.

In resolving this important preemption case, the Court should reaffirm the crucial importance of obstacle preemption and provide clearer guidance on how the implied conflict preemption inquiry should (and

should not) be conducted. Such guidance will go far toward clarifying the doctrine of implied preemption in the same way this Court's recent decisions involving express preemption have provided much-needed clarification. See, *e.g.*, *Riegel* v. *Medtronic, Inc.*, 128 S. Ct. 999 (2008).

II. The Vermont Supreme Court's decision rests on multiple legal errors. As Wyeth persuasively demonstrates, the lower court fundamentally misread the several federal statutory and regulatory provisions. *First*, Section 202 does not purport to restrict the ordinary reach of the Supremacy Clause but rather reflects Congress's intent, in passing the 1962 amendments to the FDCA, not to be understood as occupying the entire field of prescription drug regulation to the complete exclusion of the States. The lower court's reading of Section 202 should also be rejected because it is nonsensical. Why would Congress have wished to authorize state and local governments to erect obstacles to, and frustrate the purposes underlying, the Food, Drug, and Cosmetic Act and the FDA's regulatory regime relating to prescription-drug approval and labeling? Moreover, Section 202 is by its express terms limited to the 1962 "amendments." Why would Congress have wished to extinguish obstacle preemption for those amendments but not for the balance of the Food, Drug, and Cosmetic Act? The Vermont Supreme Court did not offer a plausible answer to these questions, and none exists.

Second, the lower court misread and misunderstood the FDA's labeling regulations, and in particular its CBE regulation (21 C.F.R. § 314.70). The Vermont Supreme Court incorrectly thought that Section 314.70 allowed Wyeth to make "unilateral changes to [Phenergan's] drug label[]" without obtaining prior

FDA approval "whenever [Wyeth] believes it will make the product safer." Pet. App. 13a. In fact, the FDA has long interpreted the CBE regulation as permitting changes to labeling *only* where the changes reflect *newly discovered information* about the drug's safety – information that the FDA has not previously considered. The FDA's longstanding interpretation of the CBE regulation is entitled to deference under settled principles of administrative law. See *Auer* v. *Robbins*, 519 U.S. 452, 461 (1997).

In this case, the Court should also give substantial weight to the FDA's 2006 statements relating to preemption and the adverse and disruptive effects of certain state-law product liability lawsuits on the federal regulatory scheme. See 71 Fed. Reg. 3922 (Jan. 24, 2006); Pet. App. 24a. The Court has relied on such agency statements in the past in evaluating whether state law frustrates federal law and agency programs. See *Medtronic Inc.* v. *Lohr*, 518 U.S. 470, 496 (1996); *Geier*, 529 U.S. at 883. Such reliance makes eminent sense especially where, as here, determining whether state law stands as an obstacle to a complex federal regulatory scheme requires an understanding not only of how the scheme works and affects the real-world conduct of regulated parties but also of how the imposition of diverse state and local requirements affects that scheme and those regulated parties. The FDA's statements in 2006 about the potentially disruptive and deleterious impact on the public health of certain product liability lawsuits are persuasive and thus deserving of substantial weight in this Court.

Finally, the Vermont Supreme Court was wrong to invoke, at several points in its opinion, the so-called "presumption against preemption." As the Chamber has explained in other recent cases, that presumption

is of doubtful validity generally, has been invoked by this Court (albeit inconsistently and controversially) when analyzing claims of *field* and *express* preemption, and has *no* application in cases involving implied conflict preemption. In resolving this case, the Court should make clear that the presumption is irrelevant to resolving issues of implied conflict preemption.

ARGUMENT

I. The Doctrine Of Implied Conflict Preemption Flows Directly From The Supremacy Clause, Serves A Vital Role in Our Constitutional Scheme, And Was Entrusted To Judicial Enforcement By The Framers

Federal preemption of state and local law is an ordinary, intended – and indispensable – feature of our constitutional scheme. Congress's authority to legislate preemptively pursuant to its powers enumerated in Article I of the Constitution, including the Necessary and Proper Clause, U.S. CONST. art. I, § 8, is beyond dispute and has been described by this Court as "[a] fundamental principle of the Constitution." *Crosby* v. *National Foreign Trade Council*, 530 U.S. 363, 372 (2000).[4] In scores of statutes covering a wide array of

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[4] This constitutional basis is important because it explains why the exercise of preemptive authority by Congress raises no concern under the Tenth Amendment, which provides that "[t]he powers *not delegated* to the United States by the Constitution, nor prohibited by it to the States, *are reserved* to the States respectively, or to the people." U.S. CONST. amend. X (emphasis added). "If a power *is* delegated to Congress in the Constitution, the Tenth Amendment expressly disclaims any reservation of that power to the States; if a power is an attribute of state sovereignty reserved by the Tenth Amendment, it is necessarily a power the Constitution has *not* conferred on Congress." *New York* v. *United States*, 505 U.S. 144, 156 (1992) (emphasis added).

subjects, Congress has elected to include provisions that expressly preempt state and local law.

Moreover, it is beyond dispute that Congress's handiwork has a preemptive effect even in the absence of such express preemption provisions. This result flows directly from the Supremacy Clause of the Constitution, which the Framers included to remedy glaring shortcomings in the Articles of Confederation. One legal scholar has aptly summarized those shortcomings:

> In the absence of something like the Supremacy Clause, state courts might have sought to analogize federal statutes to the law of a foreign sovereign, which they could ignore under principles of international law. . . . Article XIII [of the Articles of Confederation] had specified that "every State shall abide by the determinations of the United States in Congress assembled, on all questions which by this confederation are submitted to them." But this language did not necessarily mean that Congress's acts automatically became part of the law applied in state courts; it could be read to mean only that each state legislature was supposed to pass laws implementing Congress's directives. If a state legislature failed to do so, and if Congress's acts had the status of another sovereign's law, then Congress's acts might have no effect in the courts of that state. . . .
>
> [Moreover,] [t]he Articles had not been ratified by conventions of the people in each state; states had manifested their assent merely by passing ordinary statutes authorizing their delegates to sign the Articles, and many states had not recognized the Confederation in their own constitutions. James

> Madison fretted that as a result, "whenever a law of a State happens to be repugnant to an act of Congress," it "will be at least questionable" which law should take priority, "particularly when the latter is of posterior date to the former."

Caleb Nelson, *Preemption*, 86 VA. L. REV. 225, 247-48, 251 (2000) (quoting James Madison, *Vices of the Political System of the United States* (Apr. 1787), in 9 PAPERS OF JAMES MADISON 345, 352 (R. Rutland & W. Rachal eds. 1975)).

To address these structural deficiencies in the Articles, the Framers included the Supremacy Clause, which broadly provides that "the Laws of the United States . . . shall be the *supreme* Law of the Land . . . *any* Thing in the Constitution or Laws of *any* State *to the Contrary notwithstanding*." U.S. CONST. art. VI, cl. 2 (emphasis added). As a consequence of the Supremacy Clause, all federal laws are automatically preemptive of state and local laws to the extent that the latter impose conflicting obligations or requirements. To understand the importance and vital role of the Supremacy Clause, it is useful briefly to review its genesis during the debates in the Constitutional Convention.

A. The Origins Of The Supremacy Clause

During the Convention, the Founders considered "three mechanisms for resolving conflicts between federal and state law." Bradford Clark, *Separation of Powers As A Safeguard of Federalism*, 79 TEX. L. REV. 1321, 1348 (2001). *First*, the Virginia (or Large State) Plan proposed "authorizing the Union to use military force to coerce the states to comply with federal law." Bradford Clark, *Unitary Judicial Review*, 72 GEO. WASH. L. REV. 319, 325 (2003). But "[t]he delegates

were immediately opposed to the use of force" and "[t]he Convention tabled the proposal and never seriously entertained this alternative." *Id.* at 325-26 & nn.44-47.

Second, the Virginia Plan alternatively recommended "that the National Legislature ought to be impowered . . . to negative all laws passed by the several States, contravening in the opinion of the National Legislature the articles of Union . . . ." James Madison, *Notes on the Constitutional Convention* (May 29, 1787), in 1 THE RECORDS OF THE FEDERAL CONVENTION OF 1787, at 21 (Max Farrand ed. 1911) ("FARRAND'S RECORDS"). Under this "congressional negative" as originally proposed, Congress would have had the power to "negative" all state laws that, in Congress's judgment, violated the federal Constitution. The delegates apparently envisioned the congressional negative, by analogy to the Crown's prerogative to approve Colonial laws, as operating to *prevent* state laws from going into effect *until* Congress acted (except in special circumstances).[5]

Third, the New Jersey Plan included a resolution that "was in substance and concept, if not in form, similar to the current language of the Supremacy Clause." Viet Dinh, *Reassessing the Law of Preemp-*

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[5] See, *e.g.*, 2 FARRAND'S RECORDS 27 (Madison) (arguing that anything short of the congressional negative would be ineffective because it would allow the States to "pass laws which will accomplish their injurious objects before they can be repealed" by Congress or invalidated by the federal courts); *ibid.* (Martin) (in criticizing the proposal, posing the following rhetorical question: "Shall all the laws of the States be sent up to the Genl. Legislature before they shall be permitted to operate?"); *id.* at 390 (Mason) (voicing identical concern); 1 FARRAND'S RECORDS 167 (Bedford) (same).

tion, 88 GEO. L.J. 2085, 2089 (2000). It "would have required state courts (subject to federal appellate review) to enforce the Laws of the United States 'made by virtue & in pursuance of the powers . . . vested in them' as 'the supreme law of the respective States.'" Clark, *supra*, 72 GEO. WASH. L. REV. at 327 (quoting 1 FARRAND'S RECORDS 245).

The Convention initially approved the "congressional negative" in its original form. *Id.* at 326. But Charles Pinckney "moved to expand the negative" by giving Congress the power to negate any state law that Congress regarded as "improper" (rather than merely contrary to the federal Constitution). At that point, the small-state delegates strongly objected, and the Convention not only rejected Pinckney's proposal but also "subsequently reconsidered and rejected even the original congressional negative." *Ibid.* Even though the original congressional negative was "limited on its face," it was unacceptable to a majority of States because it "would have allowed *Congress* to determine for itself the scope of its powers vis-à-vis the states." *Ibid.* (emphasis added).

"Although th[e] 'Supremacy Clause' [in its initial form] was originally rejected as part of the New Jersey Plan, the Convention subsequently adopted the Clause immediately after rejecting the congressional negative." *Id.* at 327. In so doing, the Convention rejected the arguments of James Madison (who had been the primary drafter of the Virginia Plan) that the adoption of the congressional negative was "essential to the efficacy & security of the Genl. Govt." 2 FARRAND'S RECORDS 27. Disagreeing with Madison, Gouverneur Morris explained that any "law that ought to be negatived will be set aside *in the Judiciary departmt.* and if that security should fail; may be *repealed by a Nationl.*

law." *Id.* at 28 (emphasis added). Similarly, Roger Sherman argued that the congressional negative was "unnecessary" because the state courts "would not consider as valid any law contravening the Authority of the Union, and which the legislature would wish to be negatived." *Id.* at 27.[6]

As the foregoing history make clear, the Convention delegates who opposed the congressional negative did so because, among other things, they viewed it as unnecessary once the Supremacy Clause had been included in the Constitution. The Supremacy Clause assigned to *the courts* in the first instance the duty to ensure that state laws that were inconsistent with federal laws would be accorded no effect (and thus preempted). Failing that, Congress could always take further action by passing preemptive laws to address the situation. Thus, the delegates who were critics of the congressional negative *assumed* that Congress would have the authority to preempt state law. See also Dinh, *supra*, 88 GEO. L.J. at 2089-90 (2000) (noting that, in contrast to the congressional negative of the Virginia Plan, which was "proposed as one of Congress' affirmative powers," the Supremacy Clause "is relevant only at the post-enactment stage, where a state law conflicts to some degree with a federal law").

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[6] After the delegates had approved the Supremacy Clause, Charles Pinckney again proposed to add the congressional negative, but this time a version that would have required two-thirds of both houses. 2 FARRAND'S RECORDS 390. In response, Roger Sherman argued that this provision was "unnecessary" because, in light of the Supremacy Clause, the "laws of the General Government" will be "Supreme & paramount to the State laws." *Ibid.* The Convention then voted against committing Pinckney's proposal to committee for further study. *Id.* at 391.

Finally, the specific language of the Supremacy Clause confirms the Framers' intent that it be enforced by the Judiciary. See U.S. CONST. art. VI, cl. 2 ("This Constitution, and the Laws of the United States . . . and all Treaties . . . shall be the supreme Law of the land; and the Judges in every State shall be bound thereby; any Thing in the Constitution or Laws of any State to the Contrary notwithstanding."). The first clause establishes a hierarchy of federal law and authority; the second is expressly directed at "Judges." As for the third clause – "any Thing in the Constitution or Laws of any State to the Contrary notwithstanding" – recent scholarship has established that its form would have been understood by the Framers (and eighteenth-century judges) as a so-called "*non obstante*" clause. Such clauses were understood by the courts as a directive *not* to employ the traditional presumption against implied repeals (which might induce strained interpretations to harmonize a later federal law with an earlier state regulation), but instead to give a federal statute its most reasonable construction and allow it to displace whatever state law it contravened when so construed. See Nelson, *supra*, 86 VA. L. REV. at 232, 235-44, 291-303. The *non obstante* form of the Supremacy Clause, then, suggests that judges should *not* automatically prefer a narrow interpretation of a federal statute to avoid the conclusion that it contradicts (and hence preempts) state laws. *Id.* at 232, 245-64. In other words, the Supremacy Clause is effectively a directive to the judiciary *not* to apply any "presumption against preemption."[7]

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[7] Other scholars and learned commentators have agreed with Professor Nelson on this score. See, *e.g.*, Dinh, *supra*, 88 GEO. L.J. at 2087 ("the constitutional structure of federalism does not admit to a general presumption against federal preemption of state law");

B. This Court's Longstanding Interpretation Of The Supremacy Clause As The Source Of Obstacle And Impossibility Preemption

As explained above (at 2-4), this Court has elucidated the meaning of the Supremacy Clause in a long line of cases involving the doctrine of implied conflict preemption. These cases stretch back almost 200 years. See, *e.g.*, *Gibbons* v. *Ogden*, 22 U.S. (9 Wheat.) 1 (1824); *Houston* v. *Moore*, 18 U.S. (5 Wheat.) 1 (1820); *M'Culloch* v. *Maryland*, 17 U.S. (4 Wheat.) 316 (1819). Both obstacle and impossibility preemption have roots in these early cases. And the Court's decisions consistently have made clear that both forms of conflict preemption rest on an interpretation of the text of the Supremacy Clause itself. See, *e.g.*, *Perez* v. *Campbell*, 402 U.S. 637, 649 (1971) (obstacle preemption is an "articulation of the meaning of the Supremacy Clause").

Illustrative is *M'Culloch*, where Chief Justice Marshall explained that, by virtue of the Supremacy Clause, "the government of the Union, though limited in its powers, is supreme within its sphere of action," so that duly enacted federal statutes must prevail over contrary state laws. 17 U.S. (4 Wheat.) at 405-06, 425-26, 432, 436. Accordingly, the Court held, the State of Maryland could not exercise its general power to tax in a manner that would destroy, impede, or burden the

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Jack Goldsmith, *Statutory Foreign Affairs Preemption*, 2000 SUP. CT. REV. 175, 182 (presumption is "difficult to justify" on constitutional grounds); Paul Clement & Viet Dinh, *When Uncle Sam Steps In: There's No Real Disharmony Between High Court Decisions Backing Pre-emption And The Federalism Push of Recent Years*, LEGAL TIMES, June 19, 2000, at 66 (arguing that the presumption "finds no support in the structure of the Constitution").

operation of a specific agency created by a valid federal law (the Bank of the United States). *Id.* at 425-37. As Chief Justice Marshall explained in language suggestive of obstacle preemption, "It is of the very essence of [federal] supremacy, to remove all *obstacles* to its action within its own sphere, and so to modify every power vested in subordinate [state] governments, as to exempt its own operations from their . . . influence." *Id.* at 427 (emphasis added). See also pages 3-4 & n.2, *supra*.

C. This Court's Unwillingness To Create A Hierarchy Of Types Of Conflict Preemption And The Vital, Independent Functions Of Impossibility And Obstacle Preemption

In addition to long interpreting the Supremacy Clause as the source of both obstacle and impossibility preemption, this Court has sometimes used other verbal formulations to describe state laws that are nullified because they stand in conflict with federal law:

> This Court, in considering the validity of state laws in the light of treaties or federal laws touching the same subject, has made use of the following expressions: conflicting; contrary to; . . . repugnance; difference; irreconcilability; inconsistency; violation; curtailment; and interference. But none of these expressions provides an infallible constitutional test or an exclusive constitutional yardstick.

Hines, 312 U.S. at 67.

Notably, however, the Court has declined to draw a sharp line distinguishing between forms of conflict preemption emanating from the Supremacy Clause. In *Geier* v. *American Honda Motor Co.*, 529 U.S. 861

(2000), for example, this Court rejected the argument that a party claiming *obstacle* preemption should be required to bear a "special burden" when the relevant federal statute includes a "savings" provision:

> The Court has not previously driven a legal wedge – only a terminological one – between "conflicts" that prevent or frustrate the accomplishment of a federal objective and "conflicts" that make it "impossible" for private parties to comply with both state and federal law. Rather, it has said that both forms of conflicting state law are "nullified" by the Supremacy Clause, . . . and it has assumed that Congress would not want either kind of conflict. . . . We see no grounds, then, for attempting to distinguish among types of federal-state conflict for purposes of analyzing whether such a conflict warrants pre-emption in a particular case.

529 U.S. at 873-74 (citations omitted).[8]

This reluctance to create a hierarchy of theories of conflict preemption is understandable, not only because conflicts and inconsistencies between federal and state law can take myriad forms but also because obstacle and impossibility preemption each serve a vital function in our constitutional scheme. Impossibility preemption addresses situations where both federal and

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[8] The Court in *Geier* also gave as a reason for rejecting special treatment of obstacle preemption the fact that such an approach would "promise practical difficulty by further complicating well-established pre-emption principles that already are difficult to apply." 529 U.S. at 873. "That kind of analysis," the Court explained, "would engender legal uncertainty with its inevitable systemwide costs . . . as courts tried sensibly to distinguish among varieties of 'conflict' [preemption] (which often shade, one into the other) . . . ." *Id.* at 874.

state law impose mandates on a regulated party – and it is simply not possible to comply simultaneously with both mandates. If the federal government commands a citizen to do X and a state law requires a citizen *not* to do X (or makes doing X a crime), there is no way to comply with both the federal and state requirements. In that circumstance, the state command must yield. See, *e.g.*, *Southland Corp.* v. *Keating*, 465 U.S. 1, 10, 16 (1984) (Congress's decision to "mandate[] the enforcement of arbitration agreements" preempts California's mandate that such agreements be invalidated in certain situations).

But federal laws and regulatory regimes can be severely undermined and even destroyed even in the absence of such diametrically opposed commands or requirements. If Congress passes a law guaranteeing the right of all workers to join a union, and a State makes it a felony offense to join a union, it is *not impossible* to comply with both laws; by declining to exercise the federally created right, a worker can easily comply with both laws. But the state law in this scenario so clearly undermines and burdens the federal right to join a union – and frustrates the purpose of the federal statute, which is to safeguard the right to join a union and perhaps to encourage union membership – that it obviously cannot stand under the Supremacy Clause.

Indeed, this Court has applied obstacle preemption even when the burden imposed on federal rights was far less dramatic than in this hypothetical example. For example, in *Felder* v. *Casey*, 487 U.S. 131 (1988), the Court ruled that 42 U.S.C. § 1983 preempted a Wisconsin notice-of-claim statute that required a civil rights plaintiff to provide written notice (at least 120 days before filing suit) to putative government defendants of the circumstances giving rise to her constitu-

tional claims, the amount of the claim, and her intent to bring suit. In the absence of such notice, the Wisconsin law required the state courts to dismiss the plaintiff's Section 1983 lawsuit. Writing for the Court, Justice Brennan explained that the Wisconsin statute was barred under the doctrine of obstacle preemption because, among other things, it "burdens the exercise of the federal right by forcing civil rights victims who seek redress in state courts to comply with a requirement that is entirely absent from civil rights litigation in the federal courts." *Id.* at 141; see also *id.* at 138, 144-45. That conclusion necessarily depended on a robust doctrine of obstacle preemption, because it plainly was not impossible to comply with both the Wisconsin statute and the requirements of Section 1983. As *Felder* illustrates, the doctrine of obstacle preemption plays a vitally important role – and a role that complements impossibility preemption – in ensuring the supremacy and full effectiveness of *all* federal laws against incursions and encroachments by the States.

D. This Court's Well-Established Method Of Deciding Conflict Preemption Issues

This Court's general methodology in resolving conflict preemption issues is also well settled. "Deciding whether a state statute is in conflict with a federal statute and hence invalid under the Supremacy Clause is essentially a two-step process of first ascertaining the construction of the two statutes" – federal and state – "and then determining the constitutional question whether they are in conflict." *Perez*, 402 U.S. at 644. In conducting this inquiry, a federal court is bound by the authoritative construction given to the relevant state law by the State's courts. *Ibid.* Moreover, "[t]he relative importance to the State of its own law is *not material* when there is a conflict with valid federal law,

for the Framers of our Constitution provided that the federal law must prevail.'" *Fidelity Fed. Savings & Loan Ass'n* v. *de la Cuesta*, 458 U.S. 141, 153 (1982) (emphasis added) (quoting *Free* v. *Bland*, 369 U.S. 663, 666 (1962)).

The judicial decision as to exactly when the tension between state and federal laws rises to the level of a "conflict" is a matter of judgment. See *Crosby* v. *National Foreign Trade Council*, 530 U.S. 363, 373 (2000) ("What is a sufficient obstacle is a matter of judgment, to be informed by examining the federal statute as a whole and identifying its purpose and intended effects[.]"). The critical question in each case is the extent of the inconsistency between state and federal law and whether that amount is sufficient, under the Supremacy Clause, to trigger conflict pre-emption.

* * *

Notwithstanding (a) the deep roots of the doctrine of implied conflict preemption in the Supremacy Clause and this Court's decisions, (b) this Court's traditional unwillingness to differentiate between types of federal-state conflicts triggering operation of the Supremacy Clause, and (c) the vital, structural roles played by both obstacle and impossibility preemption in protecting the national government and federal laws from encroachment and subversion by States and localities, some Members of this Court (and some legal scholars) have expressed special concerns about applying the doctrine of obstacle preemption. For example, the dissenters in *Geier* referred to "our potentially boundless . . . doctrine of implied conflict pre-emption based on frustration of purposes" and expressed concern that obstacle preemption vests too much discretion in "unelected federal

judges." 529 U.S. 861, 894, 907 (Stevens, J., dissenting). See also REPORT OF THE APPELLATE JUDGES CONFERENCE, AMERICAN BAR ASS'N, THE LAW OF PREEMPTION 38 (1991) (obstacle preemption "demands a high degree of judicial policymaking").[9]

It is true, of course, that obstacle preemption sometimes requires judges to make subtle judgments about when the tension between state and federal law rises to the level of a preemption-triggering conflict. *Crosby*, 530 U.S. at 373. But those same types of judgments are also required for other forms of implied conflict preemption. True, obstacle preemption often requires judges to identify the congressional "purpose" that allegedly is being thwarted by state law. That task, however, is not an unfamiliar one for judges who routinely engage in the interpretation of statutes. Furthermore, Congress often declares its purposes explicitly in a statute (or in the accompanying legislative materials). Moreover, these judgment calls involve no more discretion than a wide array of other decisions made by federal courts every day. The law is filled with broad concepts – reasonableness, probable cause, excusable neglect, good cause, ordinary care – that call for the judicial exercise of judgment.

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[9] The principal author of the ABA Report has explained that his views on the doctrine of preemption have changed in response to fundamental changes in the legal landscape that have occurred since 1991. See Kenneth Starr, *Preface*, in FEDERAL PREEMPTION: STATES' POWERS, NATIONAL INTERESTS xi, xv (R. Epstein & M. Greve eds. 2007); see also *id.* at xvi (suggesting that Congress "cannot possibly police and redress every improper incursion on federal authority by legislative, executive, and judicial branches of all 50 state governments" and concluding that, "[i]f that job is to be done at all, it must be the federal judiciary that does it").

Beyond that, as the foregoing discussion of the Constitutional Convention makes clear, the Supremacy Clause is by design a provision that is meant to be *enforced by the courts* (in contrast to the rejected congressional negative, which Congress itself would have employed). Federal courts are the institutions entrusted by the Constitution with the authority to police incursions by the States on the supremacy of federal law. And the tasks that are involved in deciding an issue of implied conflict preemption under this Court's traditional methodology – interpretation of the state and federal laws in question and of the Supremacy Clause – are tasks the judiciary is uniquely suited to undertake. For all of these reasons, this Court should reject any arguments in this case that would either abandon or weaken settled principles of obstacle preemption.

II. This Court Should Reverse The Flawed Decision Below And Clarify The Doctrine Of Implied Conflict Preemption

The Chamber agrees with Wyeth that the Vermont Supreme Court's decision rests on several clear errors of law. Specifically, the lower court misinterpreted Section 202 of the Drug Amendments of 1962, Pub. L. No. 87-781, § 202, 76 Stat. 780, 793, misunderstood an important FDA labeling regulation, 21 C.F.R. § 314.70, and misidentified patient safety as Congress's sole objective in passing the FDCA. Pet. App. 20a. Once these errors are corrected, it is clear that respondent's state-law claims are preempted under both impossibility and obstacle preemption. Despite the availability of this rather narrow ground for decision, the Chamber urges the Court to take this opportunity to clarify the doctrine of implied conflict preemption in several key respects.

A. The Lower Court's Reliance On The Presumption Against Preemption Was Mistaken

In rejecting both of Wyeth's implied preemption arguments, the Vermont Supreme Court specifically invoked "the presumption against preemption." Pet. App. 14a, 23a. As Wyeth demonstrates (Pet. Br. 51 n.23), that rule of construction is irrelevant because the federal government has regulated drug labeling for more than a century. See *United States* v. *Locke*, 529 U.S. 89, 90, 108 (2000) (presumption against preemption "is not triggered when [a] State regulates in an area where there has been a history of significant federal presence").

More fundamentally, the Court should take this opportunity to make clear that the presumption against preemption – whatever its applicability to questions of field preemption – is simply inapplicable to cases involving conflict preemption. In *Warner-Lambert Co.* v. *Kent*, 128 S. Ct. 1168 (2008) (per curiam order), the Chamber filed an *amicus* brief urging this Court to resolve confusion in the lower courts by squarely holding that the presumption does *not* apply to issues of conflict preemption. See Br. of The Chamber of Commerce of the United States of America As *Amicus Curiae*, *Warner-Lambert Co. LLC* v. *Kent*, No. 06-1489, at 8-20. Without repeating all the same arguments here, the Chamber refers the Court to that brief and respectfully renews the same request. As explained above, recent scholarship establishes that the Supremacy Clause is a "*non obstante*" clause that, by its very nature, directs the courts *not* to apply any presumption against preemption. The Court's resolution of this issue would go far toward clarifying the

litigation of implied conflict preemption issues in the lower courts.

B. The Lower Court's Reading Of Section 202 Was Wrong And Nonsensical

As Wyeth persuasively shows (Pet. Br. 51-54), the Vermont Supreme Court misread Section 202 of the 1962 Amendments as extinguishing the doctrine of obstacle preemption in connection with the FDCA and leaving in place only impossibility preemption. In fact, Section 202's function was to make clear that Congress did not intend to occupy the entire field of drug regulation; and its reference to "direct and positive" conflicts was nothing more than a shorthand for implied conflict preemption. Congress thus has demonstrated an intent to *preserve* conflict preemption in all of its forms. The lower court's reading of Section 202 was wrong.

As if that were not enough, the Vermont Supreme Court's interpretation also makes very little sense. In *Geier*, this Court observed it was difficult to believe that Congress, in passing the savings clause at issue there, would "not have wanted ordinary pre-emption principles to apply where an actual conflict with a federal *objective* is at stake." *Id.* at 871 (emphasis added). To hold otherwise, this Court reasoned, would have the effect of "tak[ing] from those who would enforce a federal law the very ability to achieve the law's congressionally mandated objectives that the Constitution, through the operation of ordinary pre-emption principles, seeks to protect" – an outcome that "permits [the federal] law to defeat its own objectives, or . . . destroy itself." *Id.* at 872 (internal quotation marks omitted). The Vermont Supreme Court's reading of Section 202 suffers from a similar credibility gap. Indeed, it is worse, because Section 202 is expressly

limited to the effect of the 1962 "amendments." If that language is to be given its plain meaning, then under the Vermont Supreme Court's interpretation Congress wished to extinguish obstacle preemption with regard to the 1962 amendments but not with regard to other provisions of the FDCA. Why? The Vermont Supreme Court gave no plausible explanation, and there is none.[10]

C. The FDA's Views About The Detrimental Effects Of Recent Product Liability Litigation On Its Regulatory Regime Are Persuasive And Should Be Given Significant Weight

As Wyeth correctly explains (Pet. Br. 34-40), the Vermont Supreme Court's rejection of impossibility preemption rests on a misunderstanding of an FDA labeling regulation, 21 C.F.R. § 314.70, which the parties have referred to as the "CBE" regulation. The lower court thought that provision allowed Wyeth to make "unilateral changes to [Phenergan's] drug label[]" without obtaining prior FDA approval "whenever [Wyeth] believes it will make the product safer." Pet. App. 13a. In fact, the FDA has long interpreted the CBE regulation as permitting changes to labeling *only* where the changes reflect *newly discovered information*

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[10] Because the lower court's reading of Section 202 is plainly wrong, there is no need in this case to address the outer limits on Congress's authority to restrict by statute the doctrine of implied conflict preemption, which as explained earlier (at 2-4, 16-18) flows directly from the Supremacy Clause. Whatever those limits might be, the Court should be very reluctant to infer that Congress, in passing a generally worded provision such as Section 202, intended either to eliminate wholesale the doctrine of obstacle preemption or to authorize the states to obstruct other, more specific federal requirements that remain in place (such as the FDA's labeling requirements).

about the drug's safety – information that the FDA has not previously considered. See also U.S. Br. 13-15 (invitation brief). Because no such new information is at issue in this case, Wyeth simply was not free to alter its labeling in the way the Vermont jury concluded that state law requires.

As Wyeth also demonstrates (Pet. Br. 39), the FDA's interpretation of the CBE regulation is long-standing and entitled to deference under settled principles of administrative law. See *Auer* v. *Robbins*, 519 U.S. 452, 461 (1997). For all the same reasons that a presumption against preemption is inapplicable to the first step in any conflict preemption analysis (in which the court interprets the relevant federal and state laws), courts should apply the ordinary rules relating to deference to administrative agencies' interpretations of the statutes and regulations they administer at this first step of the analysis.

To be sure, a more difficult question arises with respect to the weight that should be given to an administrative agency's views in the *second* step of a conflict preemption analysis – the court's evaluation of the extent of the conflict between state and federal laws and its determination whether the inconsistency rises to the level of a violation of the Supremacy Clause. The Vermont Supreme Court referred to this as a "difficult question of administrative law," which arose with respect to certain statements made in 2006 by the FDA relating to preemption and the adverse and disruptive effects of certain state-law product liability lawsuits on the federal regulatory scheme. See 71 Fed. Reg. 3922 (Jan. 24, 2006); Pet. App. 24a. But the court avoided answering that "difficult question" based on its flawed readings of Section 202 and the CBE regulation.

This Court has already made clear, however, that it is entirely appropriate to afford substantial weight to the views of an administrative agency charged with implementing a comprehensive regulatory scheme in a technical area where, as here, the agency concludes, for persuasive reasons, that state regulation interferes with its regulatory regime or presents an obstacle to the achievement of federal objectives. In *Medtronic Inc.* v. *Lohr*, 518 U.S. 470 (1996), this Court explained that the FDA is "uniquely qualified to determine whether a particular form of state law stands as an obstacle to the accomplishment and execution of the full purposes and objectives of Congress . . . and, therefore, whether it should be pre-empted." *Id.* at 496 (internal quotation marks omitted). And in *Geier*, the Court deferred to the Department of Transportation's views concerning the objectives underlying an agency safety standard and the extent to which state law would pose an obstacle to the accomplishment of those objectives. See 529 U.S. at 883-84. "The agency is likely to have a thorough understanding of its own regulation and its objectives," the Court explained, "and is uniquely qualified to comprehend the likely impact of state requirements." *Id.* at 883 (internal quotation marks omitted).

This approach makes eminent sense. The determination whether state law stands as an obstacle to a complex federal regulatory scheme often requires an understanding not only of how the scheme works and affects the real-world conduct of regulated parties but also of how the imposition of diverse state and local requirements affects that scheme and those regulated parties. In many instances, as here, this will involve technical or policy-based judgments about the practical effect of state law on the efficient and effective opera-

tion of a complex statutory and regulatory scheme – judgments that an administrative agency such as the FDA is uniquely well suited to make. Thus, it would make no sense to disregard the FDA's well-founded judgments at the second step of the obstacle preemption inquiry in this case.

In any event, the FDA's statements in 2006 about the potentially disruptive and deleterious impact on the public health of certain product liability lawsuits are quite persuasive and thus deserving of substantial weight in this Court. As the FDA has explained, state-law product liability lawsuits can, in certain circumstances, "directly threaten[] the agency's ability to regulate manufacturer dissemination of risk information," "frustrate the agency's implementation of its statutory mandate," "erode and disrupt the careful and truthful representation of benefits and risks that prescribers need to make appropriate judgments about drug use," spur the communication of "risk information" that is "unsubstantiated" and warnings about "speculative risks," and "potentially discourag[e] safe and effective use of approved products." 71 Fed. Reg. 3934-35. These effects are real, and the FDA's serious concern about their impact on the public health should be accorded substantial weight in determining whether lawsuits such as this one frustrate the purposes underlying the FDCA and the FDA's labeling regulations.

CONCLUSION

The judgment of the Vermont Supreme Court should be reversed.

Respectfully submitted.

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In The
Supreme Court of the United States

Wyeth,
Petitioner,
v.
Diana Levine,
Respondent.

On Writ of Certiorari to the Supreme Court of Vermont

AMICUS CURIAE BRIEF OF THE CITIZENS COMMISSION ON HUMAN RIGHTS

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I – INTEREST OF AMICUS

Amicus Citizens Commission on Human Rights [1] (CCHR) is a non-profit, public benefit organization dedicated to investigating and exposing psychiatric violations of human rights.

CCHR's members include prominent doctors, lawyers, artists, educators, civil and human rights representatives and professionals who see it as their duty to expose and help abolish physically damaging practices in the field of mental healing. With about 250 chapters in more than 30 countries, CCHR seeks to accomplish these stated aims with like-minded individuals and groups, including politicians, teachers, healthcare professionals, government, law enforcement officers and the media.

CCHR's expertise lies in part, in the investigation and study of the misuse and unethical use of psychotropic drugs. CCHR's study includes the means by which questionable, unreliable and unscientific diagnosis and labeling of citizens as mentally ill has created an apparent epidemic of mental "illnesses," resulting in the prescription of often dangerous drugs. On behalf of its chapters, its thousands of members and in the interest of persons whose rights and freedoms will not otherwise be heard,

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[1] Letters from the parties consenting to the filing of amicus briefs have been lodged with the Clerk of the Court. In accordance with Rule 37.6, amicus states that no counsel for any party authored or participated in any manner in this brief. No entity or person, aside from amicus, made any monetary contribution to the preparation or submission of this brief.

CCHR offers a different perspective than those of the parties or other amici.

II - SUMMARY OF ARGUMENT

The central premise of the Petitioner's argument and that of other amici supporting Petitioner, is that the Food and Drug Administration (FDA) is composed of supposedly neutral experts and that it is the sole entity competent to make determinations regarding the safety and efficacy of drugs on behalf of health care practitioners, consumers and plaintiffs who have been injured by pharmaceutical companies' products.

However, substantial public record information indicates that this presumption of the FDA's singular expertise is neither accurate nor warranted. And, upon this inaccurate presumption, the health and the lives of literally millions of persons hang in the balance.

In reality, the FDA has become subverted by the industries it regulates. It is overtly attacked by whistleblowers, Congress and watchdog groups for incompetence and dishonesty. The FDA has failed to perform its duty of preventing the distribution of dangerous drugs or of adequately warning the public of the dangers of drugs once they are known. In the past several years, the Commissioner and executives of the FDA have been called on the carpet before angry Congressional committees to explain why they ordered FDA scientists not to reveal the dangers of some medications and why the FDA permits persons with blatant conflicts of interest to hold positions of great responsibility over the approval of drugs. Because the FDA has been unable to maintain its own internal ethical standards, it has been the subject of recent legislative attempts to restore order within its

ranks. As Senator Charles Grassley stated on September 20, 2006, the FDA "has lost its way and 'sold out' to the industries it is charged to regulate." [2]

Indeed, conflicts of interest by the Advisory Committee members appointed by the FDA to investigate and approve medications for distribution, have become endemic.[3] Advisory Committee members frequently receive funds from the pharmaceutical companies which manufacture the drugs upon which the committee makes determinations of safety and efficacy. The FDA is well aware of the conflicts of interest of its appointees and routinely waives the conflicts as a matter of standard practice. As a result, excessively dangerous drugs are frequently approved by the agency for general consumption and sale.

Petitioner's position that FDA infallibility trumps all other inquiry into the safety of drugs is a fiction benefiting only pharmaceutical companies. Adoption of that position could prevent millions of victims from acquiring recourse and compensation for their injuries, and would eliminate the important checks and balances necessary to restrain large corporations from seeking profit by destroying the health, happiness and even the

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[2] Press release of Senator Charles Grassley, September 20, 2006.

[3] The GAO's investigation into the FDA led to published findings in 2006 that determined that when safety experts made recommendations to the FDA they went into a "black hole or abyss," the FDA had barred experts from testifying publicly and the "FDA lacks a clear and effective process for making decisions about, and providing management oversight of, postmarket drug safety issues." Ref: "Congress should strengthen FDA, report finds," Washington Post.com, 24 Apr. 2006; "FDA ill on tracking pills," *USA Today*, 26 Apr. 2006

lives of our citizens.

III - ARGUMENT

A. FDA Conflicts of Interest Result in Questionable Determinations of Drug Safety and Efficacy

Petitioner's central thesis is that the civil verdicts of "lay jurors" regarding drug safety "would displace FDA's expert judgment" and thereby cause "second guessing" of FDA determinations regarding the safety and efficacy of a given drug. (Petitioner's Brief at 28.) Petitioner characterizes such FDA deliberations as having an omnipotent character and argues it should not be subject to question or doubt by those who must rely upon the FDA's determinations: "FDA approved drug labeling 'communicates to health care practitioners the agency's formal authoritative conclusions regarding the conditions under which the product can be used safely and effectively." (Opening Brief at 8.)

But blind faith in the infallibility – or even the good intentions – of those who make determinations on drug safety, is simply not warranted for the reasons that follow.

B. FDA Advisory Committee "Experts" Are Not Independent. Most Have Substantial Conflicts of Interest.

If the approval of a drug or class of drugs is controversial, or public safety issues are debated, the FDA typically consults a scientific Advisory Committee whose members are selected and paid by the FDA but are not FDA employees. [4] The Agency explains:

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[4] "FDA Advisory Committees: Does Approval Mean Safety?" Report from National Research Center for Women and Families; "Guidance for

> Advisory committees provide the FDA with independent opinions and recommendations from outside experts on applications to market new drugs, and on FDA policies. The marketing applications include data to show the safety and effectiveness of human drugs.... Based on this information, advisory committees may recommend approval or disapproval of a drug's marketing application. FDA generally follows an advisory committee's recommendation ..." [5]

Yet, the public record demonstrates that the FDA and its Advisory Committees typically have conflicts of interest by virtue of payments from pharmaceutical companies to the members of the committees approving the drugs. This circumstance is both condoned and even approved by the FDA. Advisory Committees composed of conflicted members have made some stellar errors of judgment, certainly resulting in the loss of many lives. Two examples out of many demonstrate the result of the FDA's refusal to inform the public of dangerous attributes of certain drugs where the Agency's "experts" were conflicted.

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the Public, FDA Advisory Committee Members, and FDA Staff: Public Availability of Advisory Committee Members' Financial Interest Information and Waivers," U.S. Food and Drug Administration, Oct. 2007.

[5] http://www.fda.gov/cder/audiences/acspage/

1. The FDA's Refusal to Warn of Suicide and Violence Caused by Antidepressants

It is now widely accepted that the class of antidepressant drugs known as "selective serotonin reuptake inhibitors" or "SSRI" drugs causes suicidal ideation, has resulted in many suicides and has resulted in many acts of violence, self mutilation and homicide. The FDA has recently issued "black box warnings" that children and young adults are particularly susceptible to the inducement of suicide and violence by SSRI drugs.[6] But the FDA and its Advisory Committee investigating SSRIs refused to acknowledge these harms for nearly 20 years, while thousands died and many lawsuits were filed against pharmaceutical companies for damages caused by this class of drugs.

In 1987, a new drug was approved by the FDA that was to have a dramatic influence on life in the western world: the antidepressant Prozac, representing the first in what became a highly profitable line of SSRI drugs. Almost immediately, numerous reports of suicidality, violence, and hostility were associated with persons taking the drug. By 1991, Prozac had the highest number of adverse drug reaction reports of any other drug in the FDA's Adverse Event Reporting System (AERS): 402 suicide attempts, 60 deaths and over 17,000 other adverse reactions. [7] And, the FDA admitted, only between 1% and

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[6] Labeling Change Request Letter for Antidepressant Medications – FDA Letter, 15 Oct. 2004; "FDA orders strong 'black box' warnings on antidepressants used by children," *Associated Press Worldstream*, 15 Oct. 2004.

[7] May 30, 1991 memo from Alan Gelberg, Acting Chief,

10% of the actual adverse events are even reported, so the actual figures could be ten times as high. [8]

In the case of Prozac, the FDA essentially ignored the Adverse Reports in its files and kept the drug on the market, resulting in other drug companies quickly copying and marketing this lucrative compound. After 4 years of inaction in policing antidepressant fatalities and attempted suicides, the FDA agreed in September 1991 to hold public hearings on SSRI drugs before its Psychopharmalogical Drugs Advisory Committee (PDAC), based on a petition from Amicus Citizens Commission on Human Rights and pressure from victims and Congress.

It would seem astonishing that the FDA would condone much less *select* persons with blatant conflicts of interests with pharmaceutical companies to sit in judgment on Advisory Committees making determinations on life and death issues regarding drug safety. But the practice was and is commonplace in this agency. The FDA's justification for inviting non-governmental employees with conflicts to vote on approval of questionable drugs, is whether the "need for the individual's services outweighs the potential for a conflict

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Surveillance & Data Processing Branch of the Center for Drug Evaluation and Research of the FDA.

[8] "Use of Anti-Malarial Drug Lariam Previously Used by Peace Corps Veterans Linked to Mental Disorders, Suicide, (Part I)," *Insight Magazine*, 21 May 2002; Marilyn Elias, "New Antipsychotic Drugs Carry Risks for Children," *USA Today*, 2 May 2006; "UK Parliament Report Re: Pharma Influence / US Regulators Comatose as 258 Fatal Suicides Linked to Neurontin," Alliance for Human Research Protection, 6 April 2005.

of interest created by the financial interest involved." [9] However, appointment to an FDA Advisory Committee carries the status of a "special employee" of the agency. Thus, the presence of a conflict of interest in performing this official duty constitutes a federal crime, and the FDA routinely provides a "waiver" of the conflict, thus shielding the conflicted member from criminal prosecution.

Although the FDA's Division of Drug Information does not make records available to the public regarding the numbers of criminal prosecution waivers provided on a yearly or ongoing basis, the watchdog group, Public Citizen, undertook a study of records from 221 FDA Advisory Committees. It found that in 73% of the Advisory Committees, at least one member had an acknowledged financial conflict of interest, the most common of which were consulting agreements, contracts, grants and investments. The study also found that in 14% of the Committees, *three-fourths* or more of the members had conflicts, and that in 22% of the Committees *over half* of the members had financial conflicts.[10] Moreover, such conflicts rarely resulted in disqualification of the member, (*id.*), as the FDA is generous in waiving responsibility for such conflicts.

The 1991 PDAC was singularly conflicted even with

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[9] "Guidance for the Public, FDA Advisory Committee Members, and FDA Staff on Procedures for Determining Conflict of Interest and Eligibility for Participation in FDA Advisory Committees," U.S. Food and Drug Administration, Oct. 2007.

[10] Peter Lurie, "Financial Conflict of Interest Disclosure and Voting Patterns at Food and Drug Administration Drug Advisory Committee Meetings." *Journal of the American Medical Association*, April 26, 2006.

these loose rules. Five of the ten Advisory Committee members had acknowledged financial interests in the pharmaceutical companies manufacturing the lucrative SSRI drugs at issue in the hearings. Each conflicted member requested and was granted a waiver of criminal prosecution.[11] Not revealed by the FDA was that two of the remaining five "non-conflicted" voting members of the Committee both held positions with the National Alliance for Research on Schizophrenia and Depression, funded by Eli Lilly – the manufacturer of Prozac, and one had received a grant of "less than $100,000" from the pharmaceutical-company funded National Alliance for Research on Schizophrenia and Depression, prior to the meeting. [12] Thus, seven of the ten PDAC members had financial conflicts of interest.

The FDA also invited six unpaid "guests" to participate in the Advisory Committee as non-voting "consultants," three of whom, the FDA admitted, also had conflicts of interest with drug companies.[13]

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[11] James Claghorn, Keh-Ming Lin, Jeffrey Lieberman, Robert Hamer and David Dunner. Statement of Michael Bernstein, Executive Secretary of the Pharmacologic Drugs Advisory Committee, September 20, 1991.

[12] Drs. Nina Scooler and Carol Tamminga. www.utsouthn western.edu/findfac/personal/0,2358,58406,00.html. At a later meeting of the PDAC, called to address the use of Prozac for the new purported illness "premenstrual dysphoric disorder," the FDA formally conceded Dr. Tamminga had conflicts but was permitted to chair the Committee because the FDA deemed that her "participation outweighs the concern that the integrity of the agency's program and operations be questioned."

[13] The other conflicted members were John Mann, Stewart Montgomery and Martin Teicher. Statement of Michael Bernstein, Executive Secretary of the Pharmacologic Drugs

At the 1991 PDAC meeting, dozens of victims and their doctors gave heart rending testimony of attempted suicides, completed suicides, murders and destruction caused by antidepressants. The Committee had thousands of adverse reaction reports, including reports of at least 60 deaths. At the culmination of the testimony, the Committee nevertheless voted that there was no "credible" evidence to support the conclusion that antidepressant drugs caused the emergence of suicidality and other violent behavior.[14] Unsurprisingly, each of the seven Advisory Committee members with financial ties to pharmaceutical companies voted that no warning should be given to doctors and users of these dangerous antidepressants. The FDA adopted the Advisory Committee's recommendations, as it normally does, and declined to issue any public warning.

To the public, it was promoted that the FDA had thoroughly evaluated the issue, and the SSRI drugs were entirely safe. In its Amicus Brief, the FDA characterizes its examinations of drugs as a "rigorous evaluation process [which]... scrutinizes everything about [each] drug – from the design of clinical trials to the severity of the side effects ....." (FDA Brief at 13.) As to the SSRI drugs, if the effects of the drug were indeed "scrutinized" and the evaluation process was indeed "rigorous," the agency ignored its responsibilities to protect the citizenry and did

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Advisory Committee, September 20, 1991.

[14] Transcript of Proceedings, Department of Health and Human Services, Public Health Service, Food and Drug Administration, Pharmacological Drugs Advisory Committee (hearing into antidepressant drugs and violence), September 20, 1991.

so in a big way.

After the 1991 hearings, thousands of people on SSRIs committed suicide, thousands tried and failed, thousands of persons experienced severe agitation, hostility, psychosis, liver damage, sexual dysfunction and a host of other maladies from these "safe and effective" drugs.

By the spring of 1999, over 2,000 suicides by Prozac users had been reported to the FDA's Adverse Reaction Reporting system, at least a quarter of which appeared to be linked to agitation and akathisia.[15] According to the FDA's own estimate, only about 1 percent of serious side effects are ever reported on its "adverse event system." This means that, as estimated by Dr. David Healy, Department of Psychological Medicine at the University of Wales, and one of the world's leading research psychopharmacologists has estimated that as many as 50,000 akathisia-related suicides had taken place by 1999. The total estimate for all SSRIs would of course be much larger.[16]

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[15] In 1985, German authorities had already expressed concern about Prozac causing akathisia and suicide, yet the FDA still approved the drug in 1987. In May 1985, a memo by the FDA's Safety Reviewer Richard Kapit stated, "It is fluoxetine's [Prozac] particular profile of adverse side effects which may perhaps, in the future give rise to the greatest clinical liabilities in the use of this medication to treat depression." According to Dr. David Healy (Answers.com), in 1986, there were already 10 reports of psychotic episodes, 2 reports of completed suicides, 13 attempted suicides, 4 seizures—including in a healthy volunteer.

[16] Richard DeGrandpre, "The Lilly Suicides," "Adbusters", May-June 2002.

Moreover the rash of "school shooters" over the past 15 years were almost uniformly found to have ingested SSRI medications before their incomprehensible and murderous acts were performed.[17] For example, 11 of the recent school shooters were taking these psychotropic drugs, resulting in 54 killed and 105 persons wounded.[18]

Many lawsuits have been filed against pharmaceutical companies arising out of harms alleged to have been caused by SSRI drugs in the wake of murdered

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[17] Toxicology information has not been revealed as to some of the more notorious school shooters, such as Columbine shooter Dylan Klebold. Eric Harris, the ring-leader in the 1999 Columbine school shooting at therapeutic levels of the SSRI Luvox in his system.

[18] Kip Kinkel: Maureen Sielaff, "Prozac Implicated in Oregon School Shooting," *The Vigo Examiner* 1998; Shawn Cooper: "Parents: Be leery of Zoloft study findings," *The Miami Herald*, 7 Sept. 2003; Eric Harris: "Struggling with Columbine's Questions," *CBS News.com*, 22 Oct. 2001; T.J. Solomon: Evelyn Pringle, "FDA Forgot a Few ADHD Drug Related Deaths and Injuries," *Media Monitors*, 20 Feb. 2006; Elizabeth Bush: Joyce Howard Rice, "School Shooter Took Mood-altering Drug," *The Washington Times*, 25 Mar. 2005; Jason Hoffman: "Granite Hills Gunman's Kin File Claim vs. County, Sheriff," *San Diego Union Tribune*, 2003; Cory Baadsgaard: "Fox On The Record with Greta Van Susteren," *Fox National News*, 25 Nov. 2002; Ryan Furlough: "Killer's mother urges peers to monitor depressed kids; She says anti-depressant led son to poison friend," *The Baltimore Sun*, 20 May 2004; Jon Romano: James V. Franco, "Appellate Division to Hear Two Local Landmark Cases," *The Record*, 30 Apr. 2007; Jeff Weise: "Mother of Jeff Weise Seeks to be Appointed Trustee," *WCCO-TV*, 26 Nov. 2005; Asa Coon: Scott Stephens and Rachel Dissell, "Who was Asa Coon?" *Cleveland Plain Dealer*, www.cleveland.com, 10 Oct. 2007.

family members and suicides. [19]

2. Conflicts of Interest by the Vioxx Advisory Committee

More recent deadly results from a conflicted Advisory Committee, concerned the approval of the Cox-2 pain-reliever, Vioxx. After numerous reports of deaths of Vioxx users, it was taken off the market not by the FDA, but by Wyeth – even though the FDA was well aware of the dangers, as addressed below. On February 16-18, 2005, the FDA held an Advisory Committee meeting to discuss the cardiovascular risk posed by Cox-2 inhibitors, which include Celebrex, Bextra and Vioxx, and whether they should be permitted to remain in the market. The Advisory Committee voted to keep all three drugs on the market.

The Center for Science in the Public Interest ("CSPI") thereafter evaluated the conflicts of 32 Advisory Committee members selected by the FDA to evaluate the drugs. CSPI research uncovered affiliations between 10 of the scientists that served on the committee and the three manufacturers of Cox-2 inhibitors. Another 17 scientists on the advisory committee had financial interests to other drug manufacturers. According to the New York Times,

> Ten of the 32 government drug advisers who last week endorsed continued marketing of the huge-selling pain pills Celebrex, Bextra and Vioxx have consulted in recent years for the drugs' makers, according to disclosures in medical journals

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[19] "Legal Alliance Formed to Fight Antidepressant Drug Manufacturers in Birth Defect Lawsuits," SYS-CON Media, September 10, 2007.

and other public records.

> If the 10 advisers had not cast their votes, the committee would have voted 12 to 8 that Bextra should be withdrawn and 14 to 8 that Vioxx should not return to the market. The 10 advisers with company ties voted 9 to 1 to keep Bextra on the market and 9 to 1 for Vioxx's return.[20]

Thus, the FDA knowingly selects persons for Advisory Committees who have conflicts of interest by virtue of receiving money from the drug companies whose products are being reviewed. The assertion that the FDA is unable to find panels of competent persons to advise on life and death issues of drug safety and efficacy who are not conflicted, seems highly implausible. Indeed, the SSRI and Vioxx catastrophes were avoidable, and represent a low point of responsibility and competence by the FDA, manifesting why checks and balances are needed to reduce the awful power the FDA seeks to exercise over consumer's lives, and what pharmaceutical companies seek to award the agency.

3. The FDA's Continuing Refusal to Eliminate Conflicts

The fact that the FDA has seen fit to file its own amicus brief, asserting that its judgments on safety and efficacy should not be examined, investigated or second guessed in civil litigation, itself manifests the need to permit such "second guessing."

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[20] *Ten Voters on Panel Backing Pain Pills Had Industry Ties*, New York Times, February 25, 2005.

From the late 1960's through the late 1970's, the FDA was taxpayer-funded and several Congressional committees were engaged in FDA oversight, regularly holding hearings and asking tough questions aimed at enforcement of the Food, Drug and Cosmetic Act. Now the FDA is literally paid "user fees" by pharmaceutical companies for making increasingly industry-favorable decisions. Starting in 1992 with implementation of the Prescription Drug User Fee Act (PDUFA), the influence of the pharmaceutical industry was greatly enhanced by this direct payment for FDA review. That funding has now reached over half a billion dollars, with the Department of Health and Human Services setting the total fee revenue amount requested from industry for fiscal year 2009 to be $510,665,000. Thus, with the passage of PDUFA in 1992, the FDA began looking upon the industry as its client – a very large paying client.

Issues over the FDA's utilization of persons with conflicts of interest have arisen in the context of Congressional investigations seeking to repair an agency out of control. In 2007, Congress passed a revision to the Prescription Drug User Fee Act to help ameliorate some of the problem identified herein, but over stringent lobbying by the FDA as well as pharmaceutical interests, the resulting legislation was inadequate to restore real independence to the Agency. Yet its purpose manifests a Congressional finding that our country faces a very severe problem in relying upon the FDA to make important determinations of safety and efficacy of drugs.

On August 4, 2008, the FDA made further public recognition of the lack of confidence in the integrity of its Advisory Committees, in an article published on its website, "FDA Announces Improved Policies

Regarding Transparency, Public Disclosure for Advisory Committees." [21] This supposedly new and improved policy did not call for the elimination of conflicts of interest of Advisory Committee members. It did not even improve the situation. Rather, the FDA announced rules which manifested its willingness to condone and embrace conflicts of interest:

> Today, FDA is instituting a cap of $50,000 as the maximum personal financial interest an advisor may have in all companies that may be affected by a particular meeting. If an advisor's personal financial interest is greater than $50,000, he or she will not be allowed to participate in that meeting. If less than $50,000, FDA officials may, in certain situations, grant a waiver, but will do so only if they determine that there is an essential need for the advisor's particular expertise.

Moreover, under this "improved" policy, the FDA directive states that "Disqualifying financial interests include only financial interests that are currently held... For example, if the employee has a $100,000 personal consulting contract that covers a five year period of work, he would be deemed to have a financial interest in the consulting contract of $20,000 per year," and would thus qualify to sit on an Advisory Committee.

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[21] Guidance for the Public, FDA Advisory Committee Members and FDA Staff on Procedures for Determining Conflict of Interest and Eligibility for Participation in FDA Advisory Committee. It is reported at http://www.fda.gov/oc/advisory/GuidancePolicyRegs/ACWaiverCriteriaFINALGuidance080408.pdf

It is no exaggeration to say that this policy would be akin to the federal judiciary announcing that it had a new standard under which any judge would "normally" (but not always) be disqualified from ruling in a case where he had accepted over $50,000 from the plaintiff unless there was an "essential need" for that jurist's expertise. But if the judge had accepted only $45,000 in the prior year, or had accepted less than $100,000 over a 5 year period he could freely preside, and the chief judge would grant him a waiver of criminal prosecution.

C. FDA Employee Whistleblowers Have Revealed That They Were Pressured to Approve Dangerous Drugs

The information provided to the FDA by pharmaceutical companies is considered by the FDA to be a commercial secret of the manufacturer. CCHR's efforts in 1991 to gain information from the FDA regarding life threatening effects of Prozac under the Freedom of Information Act was met with recalcitrance and ultimately, a refusal to reveal the vast majority of the information provided by the manufacturer – because the manufacturer asserted a commercial trade secret privilege to shield the details concerning the effects of its drug. *Citizens Commission on Human Rights v. FDA*, 45 F.3d 1325, 1327 (9th Cir. 1995)

Similarly, although the FDA collects millions of adverse reaction reports and information on pharmaceutical products, it has done almost nothing to promulgate analyses of such information to the public. By federal law, manufacturers are required and practitioners are encouraged, to report adverse effects of medications to the FDA in the context of the FDA's Adverse Event Report

System.[22] Yet while the FDA has been given information with which to inform the public with summaries and analyses of the reported adverse effects of drugs, it declines to do so, asserting it is too busy with other matters and too poor to do its job competently. Moreover, the adverse drug reaction reports available on the FDA's website as raw data are formatted in such a way that only database programmers could make any sense out of them.

Each reporting year is comprised of seven text files that need to be married up. This works out to be over 94,000 pages of coded text for each year. Yet the FDA provides this information to the public as useless raw data. The text files would need to be put into a database that permits the information in the different files (patient age, drug used, diagnosis, adverse reactions, etc.) to be linked together, reconstructing an image of the actual MedWatch report.

However, while the FDA declines to adequately inform the public of summaries of the adverse reports of drugs, it actively prevents its own employees from revealing the dangers of drugs it evaluates, threatening and punishing those that refused to be silenced.

During the same time period that the FDA was asserting its expertise to make all necessary determinations as to the safety and efficacy of Cox-2 and SSRI drugs, a Senate Committee was investigating why the FDA was pressuring its scientists to *hide* information demonstrating the dangers of SSRI drugs. In September 2004, FDA drug analyst Dr. Andrew Mosholder testified

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[22] "Reporting Adverse Experiences to the FDA," FDA's MedWatch, http://www.fda.gov/medwatch/how.htm.

2004, FDA drug analyst Dr. Andrew Mosholder testified before a Senate Committee that he was ordered by his superiors to delete material on the risks of antidepressant drugs from records he was submitting to Congress and then to conceal the deletions.[23] Worse, Dr. Mosholder was threatened with disciplinary action if he disclosed information to Congress concerning the dangers of such drugs. *Id.*

Thereafter, when the numbers of deaths attributed to ingestion of Vioxx escalated to a national flap, the Senate also held hearings on how this drug could have been approved for market. One FDA employee who testified was analyst Dr. David Graham, the Associate Director of Science and Medicine in the FDA's Office of Drug Safety, who on November 18, 2004 noted the dangers of the drug were well known in the agency, but that pressure was placed upon him by the agency to suppress and hide his concerns. [24]

Two weeks later, hearing that *The Lancet* intended to publish Dr. Graham's research on Vioxx dangers, FDA executives took the further extraordinary step of contacting the publisher and seeking to block publication of the article. [25]

Another FDA official wrote an internal e-mail stating that the manufacturer of Vioxx, "needs to know

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[23] FDA Told Its Analyst to Censor Data on Antidepressants, *Washington Post*, September 24, 2004.

[24] Testimony of David Graham, M.D., MPH, Before Senate Finance Committee, Nov. 18, 2004.

[25] *Scientist Says FDA Called Journal to Block Vioxx Article*, USA Today, November 28, 2004.

extensive media attention that this will likely provoke."[26]

Nine months after his Congressional testimony, Dr. Graham was interviewed and said despite his revelations, nothing had changed in the agency,

> The structural problems that exist within the FDA, where the people who approve the drugs are the ones who oversee the post marketing regulation of the drug, remain unchanged. The people who approve a drug when they see that there is a safety problem with it are very reluctant to do anything about it because it will reflect badly on them. They continue to let the damage occur. America is just as at risk now, as it was in November [when the testimony was given], as it was 2 years ago, and as it was five years ago. [27]

After the incidents involving Dr. Graham and other FDA scientists who were pressured to alter findings were revealed, the non-profit Union of Concerned Scientists conducted a survey of FDA scientists published in July, 2006.[28] Citing that "[a]n unprecedented level of political

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[26] *FDA Official Alleges Pressure to Suppress Vioxx Findings*, Washington Post, October 8, 2004.

[27] *David Graham: Public Health Enemy*, Robert Goldberg, April 18, 2007, at http://www.drugwonks.com/2007/04/david_graham_public_health_enemy.html.

[28] Evidence of Political Interference: Summary of the FDA Scientist Survey, July 2006; http://www.ucsusa.org/scientific_integrity/interference/fda-scientists-survey-summary.html.

interference threatens the integrity of government science," the group sent questionnaires to nearly 6,000 FDA scientists, questioning if they had been "asked, for non-scientific reasons, to inappropriately exclude or alter technical information or conclusions in an FDA scientific document." Fifteen percent of about 1,000 scientists who responded, said they had been wrongly asked to withhold or alter information or their conclusions in agency documents. Another 17% of the respondents said they had been asked by FDA officials "to provide incomplete, inaccurate or misleading information to the public, regulated industry, media or elected/senior government officials." Another 40% said they feared retaliation if they voiced concerns about product safety in public. *Id.*

The FDA's response was that the survey was a "counter-productive exercise," according to the FDA's spokesperson, Susan Bro.[29] Perhaps it was counter-productive to the Agency's public relations, but it was revelatory that the Agency resorted to unethical and heavy-handed tactics against its own scientists who balked at approval of dangerous substances to an uneducated and trusting public.

As stated by Graham in his November 2004 testimony before Congress,

> When [the FDA] division approves a new drug, it is also saying the drug is "safe and effective." When a serious safety issue arises post-marketing, their immediate reaction is almost always one of denial,

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[29] *Some US FDA Scientists Claim Interference: Survey*, Reuters, July 21, 2006.

> so there can't possibly be anything wrong with it. The same group that approved the drug is also responsible for taking regulatory action against it post-marketing. This is an inherent conflict of interest. [30]

In testimony to Congress, Dr. Graham also noted a significant philosophical underpinning to FDA analyses and the way it treats or disregards information to protect the public: that the "FDA always claims that randomized clinical trials provide the best data." Thus, whether the "randomized trials" undertaken by the drug manufacturer are good, bad, honest or falsified, the FDA assumes the data therein is accurate, and ignores real world sources of information that are *not* "randomized trials." [31]

FDA employees other than Drs. Graham and Mosholder also refused to condone the apparent manipulation of the FDA's watchdog role. One who paid the price was FDA Veterinarian Dr. Richard Burroughs, who reviewed animal drug applications at the FDA Center for Veterinary Sciences. In 1985, Burroughs headed the FDA's safety review of the controversial genetically engineered bovine growth hormone, rBGH.

According to Dr. Burroughs, Monsanto lobbied to ease strict safety testing protocols, and dropped diseased cows from rBGH test trials to skew results. Dr. Burroughs publicly criticized the FDA's handling of rBGH to Congressional and state legislatures, and in the media.[32]

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[30] Testimony of David J. Graham, MD, MPH, November 18, 2004 Mr. Chairman and members of the Committee.

[31] Testimony of David J. Graham, MD, MPH, November 18, 2004 Mr. Chairman and members of the Committee.

[32] Linn Cohen-Cole, "The Criminalization of Raw Milk,"

publicly criticized the FDA's handling of rBGH to Congressional and state legislatures, and in the media.[32] He claimed he was prevented by his superiors from investigating data submitted by industry revealing possible health problems caused by rBGH. After several years of refusing to be silenced, in November 1989, Dr. Burroughs was fired for alleged "incompetence."[33] In a 1991 article Dr. Burroughs described a change in the FDA beginning in the mid-1980s. "There seemed to be a trend in the place toward approval at any price. It went from a university-like setting where there was independent scientific review to an atmosphere of 'approve, approve, approve.'" [34]

And, as stated by Dr. Graham, "the FDA has let the American people down, and sadly, betrayed a public trust."[35] Many more examples of such misconduct are available in the public record – far too many to address in this Amicus Brief. However, these examples demonstrate why the FDA cannot be entrusted with carte blanche authority to make binding pronouncement of safety and efficacy of drugs which may not be "second guessed" by those who may be harmed.

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[32] Linn Cohen-Cole, "The Criminalization of Raw Milk," *CounterPunch*, April 26/27, 2008; Jennifer Ferrara, "Revolving Doors: Monsanto and The Regulators," *Monitor*.

[33] *Id.*

[34] Jennifer Ferrara, *Revolving Doors: Monsanto and the Regulators* "The Ecologist", http://www.monitor.net/monitor/9904b/monsantofda.html

[35] Jennifer Ferrara, *Revolving Doors: Monsanto and the Regulators* "The Ecologist", http://www.monitor.net/monitor/9904b/monsantofda.html.

D. The FDA's Questionable and Conflicted Evaluations of Drugs Must Not Preempt the Ability Of Those Harmed from Seeking Recourse

The FDA's Amicus Brief provides little reason to trust the FDA's determination of the safety of drugs. The Agency has adopted a pharmaceutical public relations argument to justify its refusal to fully reveal the potential dangers of drugs to an unsuspecting public. The FDA's Brief states, "FDA also balances the health benefits and detriments of particular labeling, in part because labeling must strike a balance between notifying users of potential dangers and not necessarily deterring beneficial uses through overwarning." (FDA Brief at 8.) Thus, the joint position of the pharmaceutical companies and the FDA is that telling consumers too much information about the potentially deleterious effects of drugs may cause a consumer to reject them or a doctor to eschew them out of concern for harm to his patients.

In short, the FDA admits to choosing to withhold information about medications from consumers and physicians because the FDA does not want to upset consumers with the full truth about drugs they might ingest. The FDA, in its wisdom, believes it knows better than you and I about what knowledge we should have about the drugs we may take and about what knowledge our physicians really need to assist us to make such decisions. Because of this entirely theoretical possibility that someone might *not* take a drug the companies wish to sell, the FDA is withholding from us all, the country's consumers, derogatory facts about drugs because we are all too stupid, too foolish, or far too easily frightened.

sell, the FDA is withholding from us all, the country's consumers, derogatory facts about drugs because we are all too stupid, too foolish, or far too easily frightened.

On behalf of Amici's many chapters and the thousands of victims who have sought assistance from CCHR to learn the truth about drug effects, it respectfully declines the FDA's supposedly benevolent withholding of important information. The common theme of aggrieved family members of persons who committed suicide caused by pharmaceutical medications or lost their health as a "side effect," is that they simply were not told and did not know this result was possible.

The FDA fights for turf to exclude the sort of intense oversight of drug safety which could only realistically be generated by the victims of pharmaceutical products in civil litigation, who have the ability to remain focused for the years necessary to gain justice. Such intense focus is lacking in the FDA, which is willing to give responsibility for important determinations to outside "experts" who are paid by the pharmaceutical companies which sponsored the drugs at issue. Only the victims of these drugs and their legal counsel would have the staying power to counter the millions of dollars the pharmaceutical companies can muster to prevent careful scrutiny.

Viewed in the historical context of the FDA's acceptance of conflicts of interest of the persons making life and death decisions over the use of drugs, its refusal to eliminate conflicts and its suppression of adverse opinion of its own employees, the FDA's position in this case is a justification for utter malfeasance. The Agency has a public trust and is expected to be above the fray of commercial interest and to act in the best interests of

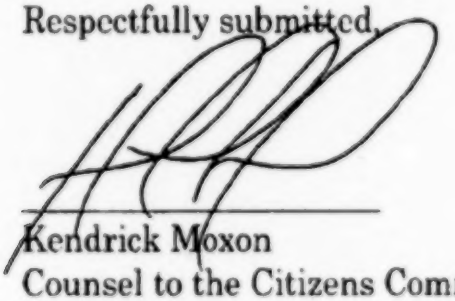
protecting consumers and saving lives. That this agency would represent it is the sole competent entity to make these important determinations on behalf of all citizens – such that its determination finally and legally *establish*,
without more, that FDA approved drugs *are* safe and effective – is a damning commentary upon our government's inability to act with integrity to provide for the health, safety and freedom of its citizens.

IV - CONCLUSION

Safety and efficacy determinations of the FDA should not be permitted to preempt the nation's citizens from seeking judicial recourse for harms caused to them by pharmaceutical companies.

Dated: August 14, 2008

Respectfully submitted,



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No. 06-1249

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IN THE

Supreme Court of the United States

WYETH,

Petitioner,

v.

DIANA LEVINE,

Respondent.

On Writ of Certiorari to the Supreme Court of Vermont

BRIEF OF THE CONSTITUTIONAL ACCOUNTABILITY CENTER AS *AMICUS CURIAE* SUPPORTING RESPONDENT

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INTEREST OF *AMICUS CURIAE* [1]

The Constitutional Accountability Center (CAC) is a think tank, law firm and action center dedicated to fulfilling the progressive promise of our Constitution's text and history. CAC works in our courts, through our government, and with legal scholars to improve understanding of the Constitution and to preserve the rights, freedoms and structural safeguards guaranteed by our Constitution.

CAC assists State and local officials in upholding valid and democratically enacted measures and historic common law remedies. Over the last decade, CAC's predecessor organization, Community Rights Counsel, filed *amicus* briefs in preemption cases before this Court in support of many State and local laws. It also has represented scores of governmental and nonprofit organizations in federal and State appellate courts across the country.

CAC seeks to preserve the careful balance of State and federal power established by the Constitution and its Amendments. CAC thus has a strong interest in this case and the development of preemption law generally.

SUMMARY OF ARGUMENT

This case presents an opportunity for the Court to clarify and reconsider its increasingly complex pre-

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[1] The parties' letters of consent to the filing of this brief have been filed with the Clerk. Under Rule 37.6 of the Rules of this Court, *amicus* states no counsel for a party authored this brief in whole or in part, and no counsel or party made a monetary contribution intended to fund the preparation or submission of this brief. No person other than *amicus curiae*, its members, or its counsel made a monetary contribution to its preparation or submission.

emption jurisprudence. The Constitutional Accountability Center submits this brief to urge the Court to reconnect the law of federal preemption to its constitutional moorings and thereby rein in—if not wholly jettison—the notion that courts are empowered to invalidate duly enacted State laws on "frustration of purposes" grounds.

Constitutional text and history do not support a general theory of implied obstacle or "frustration of purposes" preemption. In this case, the doctrine of obstacle preemption is particularly misplaced because a provision of the relevant statute regulating drug efficacy—the Federal Food, Drug and Cosmetic Act (FDCA)—specifically limits preemption to "direct and positive" conflicts with federal law. Petitioner Wyeth and its friends nonetheless assert that Respondent Levine's State common law action is preempted because it would "frustrate the purposes of federal law." Pet. Br. 29. Neither the Supremacy Clause nor the FDCA support the logic of this argument.

"Obstacle" preemption, a variant of the Court's implied conflict preemption law, has occasionally been used to preempt State laws where they frustrate the objectives of a federal enactment. However, several members of this Court have recently expressed discomfort with the "potentially boundless (and perhaps inadequately considered) doctrine of implied conflict pre-emption based on frustration of purpose." *Geier v. Am. Honda Motor Co.*, 529 U.S. 861, 907 (2000) (Stevens, J., joined by Souter, Thomas, and Ginsburg, JJ., dissenting). Such unease is warranted: a broad obstacle preemption doctrine does not fit easily into the Court's jurisprudence, given that "preemption analysis is not 'a freewheeling

judicial inquiry into whether a state statute is in tension with federal objectives,' but an inquiry into whether the ordinary meanings of state and federal law conflict." *Bates v. Dow Agrosciences LLC*, 544 U.S. 431, 459 (2005) (Thomas, J., concurring in the judgment in part and dissenting in part) (quoting *Gade v. Nat'l Solid Wastes Mgmt. Assn.*, 505 U.S. 88, 111 (1992) (Kennedy, J., concurring in part and concurring in the judgment)).

The text and history of the Supremacy Clause support these expressions of skepticism regarding implied obstacle preemption. As scholarship has demonstrated, the Supremacy Clause authorizes displacement of State law only to the extent it directly contradicts a valid federal law. No other provision of the Constitution can support a theory of obstacle preemption either. To the contrary, the text and history of the Constitution express a commitment to the preservation of State authority in traditional areas of local regulation. In addition, because any theory of implied obstacle preemption substitutes "purposes" for "laws," the doctrine improperly circumvents the specific legislative process prescribed by the Constitution. In short, "the modern doctrine of 'obstacle' preemption has no place as a doctrine of constitutional law." Caleb Nelson, *Preemption*, 86 VA. L. REV. 225, 304 (2000).

Finally, while *amicus* submits that obstacle preemption has no place in constitutional law generally, the "freewheeling" analysis into congressional purposes it entails is particularly inappropriate here, where Congress expressly limited preemption of State law under the 1962 amendments to the FDCA to instances of "direct and positive" conflicts of law. Pub. L. No. 87-781, § 202, 76 Stat. 780 (1962). Under

both the Constitution and the language of the amended FDCA, then, a State law may be preempted only where it directly contradicts federal law. This framework preserves the Court's "impossibility" variant of implied conflict preemption, which was the type of conflict contemplated by the Framers of the Supremacy Clause, while jettisoning the amorphous theory of "frustration of purposes" or obstacle preemption.

Because Respondent Levine's State common law action does not directly contradict the FDCA, it is not preempted under an impossibility analysis. Accordingly, *amicus* urges the Court to affirm the judgment of the Vermont Supreme Court.

ARGUMENT

I. THE TEXT AND HISTORY OF THE SUPREMACY CLAUSE DO NOT SUPPORT A BROAD THEORY OF IMPLIED OBSTACLE PREEMPTION.

The Supremacy Clause of the U.S. Constitution provides that: "This Constitution, and the Laws of the United States which shall be made in Pursuance thereof; and all Treaties made, or which shall be made, under the Authority of the United States, shall be the supreme Law of the Land; and the Judges in every State shall be bound thereby, any Thing in the Constitution or Laws of any State to the Contrary notwithstanding." U.S. CONST. art. VI, para. 2. The Court has applied the Supremacy Clause to preempt State laws that conflict with federal law. *E.g.*, *Brown v. Hotel & Restaurant Employees & Bartenders Int'l Union Local 54*, 468 U.S. 491, 501 (1984) (explaining that federal preemption occurs "by direct operation of the Supremacy Clause").

A. The Text Of The Supremacy Clause Makes "Laws," Not "Purposes" Or "Policies," Supreme.

The most basic problem with the doctrine of obstacle preemption is that it fails to heed precisely what it is that Article VI makes "supreme": the "*Laws* of the United States made in Pursuance [of the Constitution]." U.S. CONST. art. VI, para. 2 (emphasis added). Far from authorizing supersession of State law in the name of every federal policy or purpose, Article VI allows displacement of State law only by enacted federal *law*, which requires express agreement among two houses and two democratically-elected branches of government. *See* U.S. CONST. art. I, § 7; *INS v. Chadha*, 462 U.S. 919, 951 (1983) (finding that courts may not give effect to law that did not follow the "single, finely wrought and exhaustively considered, procedures" specified in the Constitution); *see also Thompson v. Thompson*, 484 U.S. 174, 192 (1988) (Scalia, J., concurring in the judgment) ("An enactment by implication cannot realistically be regarded as the product of the difficult lawmaking process our Constitution has prescribed."); *Bowsher v. Synar*, 478 U.S. 714, 757-759 (1986) (Stevens, J., concurring in the judgment) ("when Congress legislates, when it makes binding policy, it must follow the procedures prescribed in Article I").

The constitutionally mandated lawmaking process not only ensures that important decisions are made deliberately and democratically, but it also contains special federalism safeguards. In particular, the provision of equal State representation in the Senate in Article I, § 3, represents "a constitutional recognition of the portion of sovereignty remaining in the individual States, and an instrument for preserving

that residuary sovereignty." THE FEDERALIST No. 62, 408 (James Madison) (B. Wright ed., 1961); *accord* THE FEDERALIST, *supra*, No. 43, 315 (James Madison); *see also Garcia v. San Antonio Metro. Trans. Auth.*, 469 U.S. 528, 551 (1985) ("The significance attached to the States' equal representation in the Senate is underscored by the prohibition of any constitutional amendment divesting a State of equal representation without the State's consent. Art. V"). To permit displacement of State law by judicially imputed policies is to deny States their main "protect[ion] from [federal] overreaching" and circumvent "the principal means chosen by the framers to ensure the role of the States in the federal system." *Garcia*, 469 U.S. at 550-51 & n.11 (citing, *inter alia*, Herbert Wechsler, *The Political Safeguards of Federalism: The Role of the States in the Composition and Selection of the National Government*, 54 COLUM. L. REV. 543 (1954)); *see also id.* at 556 ("the built-in restraints that our system provides through state participation in federal governmental action . . . . ensures that laws that unduly burden the States will not be promulgated."); *see generally* Bradford R. Clark, *Separation of Powers as a Safeguard of Federalism*, 79 TEX. L. REV. 1321, 1328-36 (2001).

B. The Historical Purposes Of The Supremacy Clause Do Not Include Broad And Unpredictable Displacement Of State Laws Based On Judicially Discovered "Purposes" Or "Principles" Of Federal Law.

Historical research demonstrates that the Supremacy Clause was intended by the Framers to serve several fundamental purposes in the Constitution, none of which permits the broad and unpredictable

displacement of State law that modern "obstacle" preemption doctrine claims it effects.

First, the Supremacy Clause ensures that valid treaties and federal statutes would be treated by the States as part and parcel of their own law, and not as the law of a foreign sovereign. *See* Akhil Reed Amar, *Of Sovereignty and Federalism*, 96 YALE L.J. 1425, 1510 (1987); *see also* Lauren K. Robel, *Sovereignty and Democracy: The States' Obligations to Their Citizens Under Federal Statutory Law*, 78 IND. L.J. 543, 559 (2003). This aspect of the Supremacy Clause corrected deficiencies in the Articles of Confederation, which granted law- and treaty-making power to the United States Congress, but failed to make clear that these acts were automatically effective in the States. James Madison, Vices of the Political System of the United States (Apr. 1787), in 9 PAPERS OF JAMES MADISON 345, 352 (Robert A. Rutland & William M.E. Rachal eds., 1975) (noting that in general "the acts of Cong[res]s [under the Articles of Confederation] . . . depen[d] for their execution on the will of the state legislatures").

Second, the Supremacy Clause establishes that federal law is "supreme" and has substantive priority over State law. While it is this aspect of the clause that is often assumed to authorize implied "obstacle" preemption, history belies this interpretation. Rather, the supremacy language addressed a different and narrower problem: the concern that, under the traditional rule of temporal priority, State laws could be deemed to supersede or repeal prior federal enactments. *See* Nelson, *supra* at 250-54. Because this traditional rule of temporal priority had not been expressly modified under the Articles of Confederation, James Madison noted that "'[w]henever a law

of a State happens to be repugnant to an act of Congress,' it 'will be at least questionable' which law should take priority, 'particularly when the latter is of posterior date to the former.'" PAPERS OF JAMES MADISON, *supra* at 352. However, while the Supremacy Clause altered the substance of this conflict of laws rule, making valid federal law supreme over a subsequently enacted State law, it did not affect its domain: both the traditional rule and its constitutional successor "com[e] into play *only* when courts cannot apply both state and federal law, but instead must choose between them." Nelson, *supra* at 251. *See also* Viet D. Dinh, *Reassessing the Law of Preemption*, 88 GEO. L.J. 2085, 2087-88 (2000) (reviewing the enactment history of the Supremacy Clause and describing the clause as a "constitutional choice of law rule that gives federal law precedence over conflicting state law").

Professor Nelson summarizes the meaning of the Supremacy Clause as follows:

> Taken as a whole, the Supremacy Clause says that courts must apply all valid rules of federal law. To the extent that applying state law would keep them from doing so, the Supremacy Clause requires courts to disregard the state rule and follow the federal one. But this is the extent of the preemption it requires. Under the Supremacy Clause, any obligation to disregard state law flows entirely from the obligation to follow federal law.

Id. at 252.[2]

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[2] Professor Nelson also argues that the Supremacy Clause has a third purpose: to establish a rule of construction—a *non obstante* clause—that would prohibit courts from reading federal

Petitioner Wyeth and its *amici* offer no explanation of how modern "frustration" preemption, ostensibly pursued under authority of the Supremacy Clause, can be reconciled with the Constitution's text and history. While the Chamber of Commerce's brief in support of Wyeth quotes at length some of the same scholarship discussed in this brief, it isolates the reasoning of the quoted language from its conclusion. *Compare* Chamber Br. 13-14 (quoting at length Professor Nelson's historical analysis of the Supremacy Clause) *with* Nelson, *supra* at 265 (explaining that this historical analysis of the Supremacy Clause demonstrates the "failure of any general doctrine of 'obstacle' preemption"). The Chamber laments what it calls a "misguided assumption that obstacle preemption is somehow less important or entitled to less respect under the Supremacy Clause." Chamber Br. 9. But as the scholarship cited in the Chamber's own brief demonstrates, a proper reading of the Supremacy Clause does not merely render the "frustration prong" a poor relation, it establishes that it has no legitimate place in preemption doctrine. *Compare* Chamber of Commerce Br. 13-14, 18 *with* Nelson,

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statutes narrowly in order to harmonize them with state laws. Nelson, *supra* at 254-60. Nelson views this *non obstante* clause as evidence against the presumption against preemption that has been applied by this Court. Some members of the Court similarly reject a presumption against preemption. *See, e.g.*, *Engine Mfrs. Ass'n v. S. Coast Air Quality Mgmt. Dist.*, 541 U.S. 246, 256 (2004) (noting that "not all Members of this Court agree" on the "application" of the "presumption against preemption") (internal quotation marks omitted). Because *amicus* believes that the Court may affirm the judgment below without relying upon the presumption against preemption, that question—and this aspect of Professor Nelson's scholarship—is not addressed in this brief.

(concluding that "obstacle preemption has no place as a doctrine of constitutional law").

II. IMPLIED OBSTACLE PREEMPTION UNDERCUTS THE CONSTITUTION'S CAREFULLY CRAFTED ALLOCATION OF FEDERAL-STATE AUTHORITY.

The open-ended, judicially enforced "purpose frustration" theory of preemption embraced by Petitioner and its *amici* is not only contrary to the text and history of the Supremacy Clause, it also risks upsetting the Constitution's carefully crafted federal-state balance of power.

As this Court has long recognized, the enumeration of powers in Article I, reinforced by the Tenth Amendment, make clear the intent to preserve the authority of States, thereby "assur[ing] a decentralized government that will be more sensitive to the diverse needs of a heterogeneous society; increas[ing] opportunity for citizen involvement in democratic processes; [and] allow[ing] for more innovation and experimentation in government." *Gregory v. Ashcroft*, 501 U.S. 452, 458 (1991).[3] Respect for the Constitu-

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[3] The United States, arguing in support of broad implied obstacle preemption, ignores these well-established principles of federalism and suggests that the presence of the Supremacy Clause in the Constitution makes it unlikely that federal law would be so "self-negating" as to allow State law to operate in frustration of certain unspoken congressional objectives. U.S. Br. 30. However, robust federalism strengthens our constitutional government. *See, e.g.*, *Younger v. Harris*, 401 U.S. 37, 44 (1971) (explaining that federalism is not "blind deference to 'States Rights'" but is instead based on "the belief that the National Government will fare best if the States and their institutions are left free to perform their separate functions in their separate ways.").

tion's structural safeguards has become even more imperative as Congress has in recent years asserted itself in countless fields that historically have been the primary domain of State law. *See Gonzales v. Raich*, 545 U.S. 1, 17 (2005) (confirming Congress's "power to regulate purely local activities" that substantially affect interstate commerce). Courts should be particularly hesitant to hold that federal policies are "supreme" when the effect is to invalidate State laws on matters of historic State primacy.[4]

A doctrine that substitutes "policies" for "laws" in Article VI—and thereby authorizes judicial displacement of State laws on that basis—is also inconsistent with basic principles of deliberation and democratic accountability expressed in Article I and Article III.

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[4] Preemption of common law remedies—especially remedies for personal injury—is particularly problematic. There are important historical differences between common law remedies and other forms of state "regulation." Neither the Framers nor the 1962 Congress would have imagined that a statute like this—which provides no alternative remedy—would extinguish a traditional judicial remedy for injured parties. *See Riegel v. Medtronic, Inc.*, 128 S. Ct. 999, 1015 (2008) (MDA's failure to create any federal compensatory remedy "suggests that Congress did not intend broadly to preempt state common-law suits grounded on allegations independent of FDA requirements.") (citing *Silkwood v. Kerr-McGee Corp.*, 464 U.S. 238, 251 (1984)); *Bates v. Dow Agrosciences LLC*, 544 U.S. 431, 449 (2005) ("The long history of tort litigation against manufacturers of poisonous substances adds force to the basic presumption against preemption. If Congress had intended to deprive injured parties of a *long* available form of compensation, it surely would have expressed that intent more clearly."). The Framers, who, after all, constitutionalized a right to *jury trials* in civil cases, had a much greater tolerance for unscientific judgment and nonuniformity than petitioner and its *amici* seem to appreciate. *See* Akhil Reed Amar, THE BILL OF RIGHTS 91-118 (1998).

Although courts have established means of discerning the meaning of laws, there is no similarly reliable method of determining the "policies" of a statute. *See Thompson*, 484 U.S. at 192 (Scalia, J. concurring) ("It is at best dangerous to assume that all the necessary participants in the law-enactment process are acting upon the same unexpressed assumptions. And likewise dangerous to assume that, even with the utmost self-discipline, judges can prevent the implications they see from mirroring the policies they favor"); *see also Riegel*, 128 S. Ct. at 1009 ("It is not our job to speculate upon congressional motives."). Because many federal statutes can be said to embody "countless policies," *Pension Benefit Guar. Corp. v. LTV Corp.*, 496 U.S. 633, 646 (1990), it would be particularly inappropriate to allow a judicial search for ambiguous congressional purposes to trump the longstanding laws of the sovereign States. *See Gregory*, 501 U.S. at 464 (declining "'to give the state-displacing weight of federal law to mere congressional *ambiguity*'") (quoting Laurence H. Tribe, AMERICAN CONSTITUTIONAL LAW § 6-25, 480 (2d ed. 1988)); Kenneth Starr, et al., THE LAW OF PREEMPTION: A REPORT OF THE APPELLATE JUDGES CONFERENCE, 36 (ABA 1991) (criticizing the "purpose inquiry" in preemption cases because "a complex of competing legislative policies can be undermined").

Broad "frustration of purposes" preemption also encourages Congress to delegate the question of preemption to the courts, allowing legislators to avoid the often difficult process of achieving consensus on preemption (as well any political consequences). Indeed, a broad implied preemption doctrine threatens to render the constitutionally prescribed process for enacting laws a "tryout on the road," with implied preemption litigation the "main event." In a regime

where "policies" can have broader preemptive effect than duly enacted statutory text, those who favor controversial and expansive preemption proposals will fight battles over the contents of the legislative history, rather than the text of the enacted statute, thus achieving through the courts what they could not do in the legislature.[5] *Compare Thompson*, 484 U.S. at 192 (Scalia, J., concurring) (noting that "conscientious legislators cannot relish" a situation "where the existence or nonexistence of a private right of action depends upon which of the opposing legislative forces may have guessed right as to the implications the statute will be found to contain") *with* Roderick M. Hills, Jr., *Against Preemption: How Federalism Can Improve the Federal Legislative Process*, 82 N.Y.U. L. REV. 1, 28-29 (2007) (suggesting that some legislators may have little objection to being spared the need to cast a vote on a "politically troublesome" preemption question).

Finally, because States will be uncertain whether local regulatory regimes or causes of action will be preempted by the courts based on an amorphous theory of "obstacle" preemption, State and local innovation—which has been praised since the Founding—will be chilled.

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[5] Questions of constitutional legitimacy aside, an untethered "obstacle" preemption inquiry serves no practical purpose in the lawmaking process and may, in fact, be corrosive. Congress is fully able to express its intent to preempt State law, as attested by scores of express preemption provisions, and there is no reason to expect that the interests favoring preemption of state tort law—often including well-organized business groups like the *amici* urging *implied* preemption here—suffer from systematic disadvantages in the legislative process. *Cf. United States v. Carolene Products Co.*, 304 U.S. 144, 152 n.4 (1938).

This stark incompatibility with fundamental constitutional principles has contributed to recent concerns expressed by members of the Court about the legitimacy of implied "obstacle" preemption. In a path-marking concurrence in *Gade v. National Solid Wastes Management Association*, Justice Kennedy proposed replacing the broad form of implied obstacle preemption embraced by the majority in that case with one authorizing displacement only of those "state laws which impose prohibitions or obligations which are in direct contradiction to Congress' primary objectives, as conveyed with clarity in the federal legislation." 505 U.S. 88, 111 (1992) (Kennedy, J., concurring in part and concurring in the judgment). In *Geier v. American Honda Motor Co.*, four Justices highlighted the doctrine's "potentially boundless" character and observed that its legitimacy had been "perhaps inadequately considered." 529 U.S. 861, 907 (2000) (Stevens, J., joined by Souter, Thomas, and Ginsburg, JJ., dissenting). As that opinion explained, allowing preemption on "purpose frustration" grounds raises "the risk that federal judges will draw too deeply on malleable and politically unaccountable sources such as regulatory history in finding pre-emption based on frustration of purposes." *Id.* at 908 n.22. More recently, in *Bates v. Dow Agrosciences*, Justice Thomas (joined by Justice Scalia) approvingly noted the "Court's increasing reluctance to expand federal statutes beyond their terms through doctrines of implied pre-emption," 544 U.S. 431, 459 (2005) (Thomas, J., concurring in the judgment in part and dissenting in part), explaining that preemption analysis should be limited to an "inquiry into whether the ordinary meanings of state and federal law conflict.'" *Id.* (quoting *Gade*, 505 U.S. at 110 (Kennedy, J., concurring)).

Amicus urges the Court to take this opportunity to reconsider preemption based on "frustration of purposes" and clarify the limits of implied conflict preemption. Not only is the doctrine unsupported by the text and history of the Supremacy Clause, but it runs counter to the principles and structure of our Constitution.

III. IMPLIED OBSTACLE PREEMPTION IS PARTICULARLY INAPPROPRIATE HERE, BECAUSE CONGRESS LIMITED THE PREEMPTIVE SCOPE OF THE AMENDED FDCA TO "DIRECT AND POSITIVE" CONFLICTS.

Even if the Court were to preserve some variant of implied obstacle preemption, it would be inappropriate to apply it here. The savings clause adopted by Congress as part of the 1962 amendments to the FDCA specifically limits the preemptive scope of the amended statute to "direct and positive" conflicts. Pub. L. No. 87-781, § 202, 76 Stat. 780, 793 (1962).[6] This language demonstrates that, when undertaking to regulate the efficacy of pharmaceuticals through new drug applications, Congress intended to preserve State law unless it directly contradicted the FDCA; in other words, Congress sought to have State law preempted only where it would be impossible to comply with both federal and State law.

---

[6] Section 202 provides:

> Nothing in the amendments made by this Act to the Federal Food, Drug, and Cosmetic Act shall be construed as invalidating any provision of State law which would be valid in the absence of such amendments unless there is a direct and positive conflict between such amendment and such provision of state law.

Respondent's *amici* have detailed the legislative history and context that demonstrate that Congress intended this "direct and positive" conflict language to limit the preemptive scope of the amended statute. *E.g.*, Br. of Vermont, et al. 34-37 (explaining how § 202 borrowed language from other legislation pending at the same time, which limited preemption to the extent "there is a direct and positive conflict between such provisions so that the two cannot be reconciled or consistently stand together"). Where Congress has expressly limited preemption to cases where there is a "direct and positive" conflict, it is especially inappropriate to preempt State law based on claims of frustration of legislative purposes. *See Cipollone v. Liggett Group, Inc.*, 505 U.S. 504, 517 (1992) (applying "the familiar principle of *expressio unius est exclusio alterius*" and finding that "Congress' enactment of a provision defining the pre-emptive reach of a statute implies that matters beyond that reach are not pre-empted"), *quoted in Freightliner Corp. v. Myrick*, 514 U.S. 280, 288 (1995) (declining to find express or implied preemption of State law where no contrary federal standard existed).

While the policy objectives underlying the FDCA are surely countless, Congress made one objective clear: it did not want to displace a broad swath of State law under a hazy notion of implied obstacle preemption. Congress expressly preempted State law in other provisions of the Act, as in the Medical Devices Act preemption clause at issue in *Riegel*, but did not choose to do so for the FDCA as a whole. *See Riegel*, 128 S. Ct. at 1009 (noting that "Congress could have applied the [medical devices] pre-emption clause to the entire FDCA . . . but instead wrote a preemption clause that applies only to medical devices"). Accordingly, the doctrine of implied obsta-

cle preemption is just as out of step with the facts of this case as it is with the text and history of the Constitution.

* * *

Without recourse to the vague "frustration of purposes" theory of preemption, Petitioner is left with its argument that Vermont's common law remedy directly and positively conflicts with the FDCA because it is impossible to comply with FDA regulations and state common law duties. As Respondent's brief forcefully demonstrates, "impossibility preemption" does not apply here because Wyeth retained the ability to preclude the "IV push" method of administering Phenergan and the FDA's prior approval of a label that simply warned of the dangers associated with that method is not incompatible with a state law remedy for wrongfully injured persons. Respondent's Br. 31-43; *see also* Br. of Vermont, et al. 6-11 (explaining that federal drug labeling laws have coexisted with state common law damages claims for over 70 years). Because Wyeth has failed to show that it is impossible to comply with Vermont common law and federal drug labeling law, the Court should decline to find preemption.

CONCLUSION

The judgment of the Vermont Supreme Court should be affirmed.

Respectfully submitted,

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IN THE
Supreme Court of the United States

06-1249

WYETH,

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v.

DIANA LEVINE,

Respondent.

On Writ of Certiorari to
the Vermont Supreme Court

BRIEF OF *AMICUS CURIAE* CONSTITUTIONAL AND ADMINISTRATIVE LAW SCHOLARS IN SUPPORT OF RESPONDENT

Interest of Amici

Amici are scholars who teach and write about federal preemption of state law.[1] Mindful of the gap

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[1] Counsel for all parties have consented to the filing of this brief, and those consents are on file with the Clerk of the Court. Pursuant to Rule 37.6, *Amici* affirm that no counsel for a party authored this brief in whole or in part, that no such counsel or party made a monetary contribution to the preparation or submission of this brief, and that no person other than *Amici* and their counsel made such a monetary contribution.

that sometimes exists between the academy and the concerns of the bench and bar, we seek to bring our scholarship to bear on the particular preemption questions at issue in this case.

Our scholarly interest in preemption arises from teaching and writing in a variety of related fields, including constitutional law, administrative law, health law, and torts. Lynn E. Blais is a Professor of Law at the University of Texas School of Law, where she teaches Administrative Law. William W. Buzbee is a Professor of Law at Emory University School of Law, where he teaches Administrative Law. Philip Frickey is the Alexander F. & May T. Morrison Professor of Law at the University of California, Berkeley, School of Law, where he teaches Legislation and Constitutional Law. Thomas O. McGarity holds the Joe R. and Teresa Lozano Long Endowed Chair in Administrative Law at the University of Texas, where he teaches Environmental Law and Torts. Paul E. McGreal is a Professor of Law at the Southern Illinois University School of Law, where he teaches Constitutional Law. Nina Mendelson is a Professor of Law at the University of Michigan Law School, where she teaches Administrative and Environmental Law. Theodore Ruger is Professor of Law at the University of Pennsylvania Law School, where he teaches Constitutional Law, Food and Drug Regulation, and Health Law. Neil S. Siegel is Associate Professor of Law at Duke Law School, where he teaches Constitutional Law. Wendy E. Wagner is the Joe A. Worsham Centennial Professor at the University of Texas, where she teaches Environmental Law and Torts. Ernest A. Young is a

Professor of Law at Duke Law School, where he teaches Constitutional Law and Federal Courts.

Summary of Argument

This case implicates three critical issues in the law of preemption. First, Petitioner's amici have launched a broad attack on this Court's longstanding "presumption against preemption," *Rice v. Santa Fe Elevator Corp.*, 331 U.S. 218, 230 (1947), arguing that it is generally inconsistent with the original understanding of the Supremacy Clause and, in any event, inapplicable in conflict preemption cases. We argue, to the contrary, that the *Rice* presumption is not inconsistent with the original understanding of the Supremacy Clause, and it plays an essential role of protecting state autonomy in a world where national regulatory authority has been construed much more broadly than the Framers anticipated. Likewise, the claim that *Rice* does not apply to cases of conflict preemption misconstrues how conflict analysis actually operates and overlooks extensive precedent for such application.

The second issue concerns the preemptive effects of federal regulatory regimes that involve federal administrative approval of a product before that product can be marketed. There is no basis for construing federal premarket approval of drugs to preempt state common law liability for failures to warn. Despite a history of high profile tort litigation involving drugs, consistent efforts by industry to secure an express preemption clause similar to that in the Medical Devices Amendments (MDA), and recent statutory amendments to other aspects of the drug regime, the Food, Drug, and Cosmetic Act continues to include no express preemption provision.

Congress's evident desire to maintain state law as a supplement to federal regulation forecloses claims of conflict preemption as well. That desire is commendable, moreover, in light of serious doubts about the adequacy of the FDA's capacity to monitor drug safety after the initial approval of a drug.

Finally, this case implicates a broad set of issues concerning preemptive actions and interpretations by federal administrative agencies. This Court should accord little or no deference to the FDA's position that preemption is warranted. That position is a 180-degree reversal of the agency's longstanding view that state law provided a valuable supplement to federal regulation, and the new policy lacks the procedural indicia that this Court has generally required as a predicate to deference. Instead, the FDA's "preemption preamble" represents an effort to achieve tort reform by regulation following Congress's refusal to endorse such efforts. Congress's intent remains the touchstone for *all* forms of preemption, and that intent cannot support preemption here.

Argument

I. The Presumption Against Preemption Applies in This Case.

This Court first articulated a "presumption against preemption" in statutory construction in *Mintz v. Baldwin*, 289 U.S. 346, 350-52 (1933), and *Rice*, 331 U.S. at 229-36. The canonical statement occurs in *Rice*: "the historic police powers of the States [are] not to be superseded by [federal statute] unless that was the clear and manifest purpose of Congress." *Id.* at 230. Although Petitioner's *amici*

have challenged the *Rice* presumption's legitimacy and sought to narrow its scope, those arguments should be rejected.

A. The *Rice* Presumption Is a Critical Component of This Court's Federalism Jurisprudence.

We have articulated the case for a strong presumption against preemption at greater length in our *amicus curiae* brief in *Philip Morris USA Inc. v. Good*, which is also before the Court this Term.[2] We summarize those arguments briefly here. This Court's Commerce Clause jurisprudence leaves most areas of regulatory concern subject to concurrent national and state authority, with the result that the most critical federalism questions concern not so much what Congress *can* do, as a matter of constitutional power, but what it *has* done—and how much room it has left for state regulation. *Compare, e.g., Gonzales v. Raich*, 545 U.S. 1 (2005) (construing Congress's commerce power broadly to reach homegrown medical marijuana), *with Gonzales v. Oregon*, 546 U.S. 243 (2006) (construing the Controlled Substances Act *not* to authorize the Attorney General to preempt Oregon's Death with Dignity Act). Historically speaking, the *Rice* presumption developed as a response to the expansion of Congress's commerce power during the New Deal period: as the scope of Congress's action expanded, it was essential to ensure that federal

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[2] *See* Br. of *Amicus Curiae* Constitutional and Administrative Law Scholars in Support of Respts., No. 07-562, *Philip Morris USA Inc. and Altria Group, Inc. v. Good* (filed June 18, 2008). We incorporate the arguments of that brief here by reference.

activity did not displace too much state law. *See* Stephen A. Gardbaum, *The Nature of Preemption*, 79 CORNELL L. REV. 767, 806-07 (1994).

Moreover, the *Rice* presumption fits well with this Court's recognition that structural and political safeguards play a critical role in protecting state autonomy against federal encroachments. *See Garcia v. San Antonio Metro. Trans. Auth.*, 469 U.S. 528, 550-54 (1985). In *Gregory v. Ashcroft*, this Court explained:

> [I]nasmuch as this Court in *Garcia* has left primarily to the political process the protection of the States against intrusive exercises of Congress' Commerce Clause powers, we must be absolutely certain that Congress intended such an exercise. "To give the state-displacing weight of federal law to mere congressional *ambiguity* would evade the very procedure for lawmaking on which *Garcia* relied to protect states' interests."

501 U.S. 452, 464 (1992) (quoting Laurence Tribe, *American Constitutional Law*, § 6-25, at 480 (2d ed. 1988)). Requiring clear evidence of Congress's intent to alter the federal balance—whether by regulating the qualifications of state officers, as in *Gregory*, or by displacing state law through preemption—is important in two respects. It provides a *political* check, by providing notice to the States' representatives in Congress, and a *procedural* check, by requiring that state-displacing choices overcome

the Constitution's built-in hurdles to federal legislative action.[3]

As *Gregory* suggests, the *Rice* presumption is one of many rules of construction that protect state autonomy. *See, e.g.*, *Arlington Cent. Sch. Dist. Bd. of Educ. v. Murphy*, 548 U.S. 291, 296 (2006) (requiring that Congress clearly state conditions on grants of federal funds to the States); *Jones v. U.S.*, 529 U.S. 848, 858 (2000) (requiring a clear statement of Congress's intent to regulate at the outer limits of its Commerce Clause authority); *Will v. Mich. Dep't of State Police*, 491 U.S. 58, 65 (1989) (requiring a clear statement of Congress's intent to subject states to liability under federal statutes).[4] Because preemption questions arise so frequently, however, the *Rice* presumption is the most important of these rules.

This Court has sometimes—but not always—sought to limit the *Rice* presumption to fields that the States have "traditionally occupied." *Compare, e.g.*, *U.S. v. Locke*, 529 U.S. 89, 108 (2000) ("[A]n assumption of nonpre-emption is not triggered when the State regulates in an area where there has been a history of significant federal presence."), *with Medtronic, Inc. v. Lohr*, 518 U.S. 470, 485 (1996) (stating that *Rice* applies "[i]n all pre-emption cases"). We think the *Medtronic* position is more workable, because competent lawyers can almost

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[3] *See generally* Bradford R. Clark, *The Separation of Powers as a Safeguard of Federalism*, 79 TEX. L. REV. 1321, 1330 (2001).

[4] *See generally* Thomas W. Merrill, *Rescuing Federalism After Raich: The Case for Clear Statement Rules*, 9 LEWIS & CLARK L. REV. 823 (2005).

always characterize a case as falling within a traditional field of national *or* state regulation to suit their purposes. Here, for example, Petitioner asserts that *Rice* does not apply because "[r]egulation of drug labeling has now been the domain of the Federal Government for more than a century," Petr.'s Br. at 51 n.23. But this Court has characterized its prior decision in *Medtronic*—which also involved FDA oversight of safety—as a "case involving medical negligence, a subject historically regulated by the States." *Locke*, 529 U.S. at 108. It was precisely this difficulty in defining boundaries between national and state fields of authority that led this Court to give up its restrictive reading of the Commerce Clause after 1937.

The truth is that medical drugs and devices—like virtually every other field of regulation—have seen a significant presence of *both* state and federal regulators for some time now. Prior 2002,[5] the FDA took the position that its approvals of drugs did *not* preempt traditional state regulation through the tort system. *See infra* at Part II(B) & fn.18. If a significant history of state regulation is enough to trigger the presumption against preemption, then this case fits the bill. If a significant *federal* presence suffices to oust the *Rice* rule, then that rule can have virtually *no* remaining applications.[6] *But see Bates*

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[5] *See Amicus* Br. for U.S. in support of Defendant-Appellant (Sept. 10, 2002), *Motus v. Pfizer, Inc.*, 358 F.3d 659 (2004), 2002 WL 32303084; *see* Mary J. Davis, *The Battle Over Implied Preemption: Products Liability and the FDA*, 48 B.C.L. REV. 1089, 1094 n. 32 (2007_.

[6] *Cf. Hillsborough County v. Automated Med. Labs., Inc.*, 471 U.S. 707, 719 (1985) ("Undoubtedly, every subject that merits

v. Dow Agrosciences LLC, 544 U.S. 431, 437, 449-450 (2005) (applying the presumption to preemption analysis under the Federal Insecticide, Fungicide, and Rodenticide Act's "comprehensive regulatory scheme"). After all, the Federal Government is significantly—but hardly exclusively—involved in almost every field, from family law,[7] to primary education,[8] to land use regulation.[9]

B. The Longstanding *Rice* Presumption is Consistent with the Supremacy Clause.

Petitioner's *amici*—with the significant exception of the United States—would go further and hold the *Rice* presumption unconstitutional on the ground that it is inconsistent with the original understanding of the Supremacy Clause. This radical position is based in part on an account of the Clause's drafting history. Br. of the Chamber of Commerce of the United States of America as *Amicus Curiae* in Support of Petr. ("Chamber Brief"), at 14-17. As Petitioner's *amici* demonstrate, the Constitutional Convention adopted the Supremacy Clause only after rejecting James Madison's proposal

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congressional legislation is, by definition, a subject of national concern.").

[7] *See, e.g.*, Defense of Marriage Act, Pub. L. 104-199, 110 Stat. 2419 (1996); Child Abuse, Domestic Violence, Adoption and Family Services Act of 1988, Pub. L. 100-294, 102 Stat. 102 (1988).

[8] *See, e.g.*, No Child Left Behind Act of 2001, Pub. L. 107-110, 115 Stat. 1425 (2001); Elementary and Secondary Education Act of 1965, Pub. L. 89-10, 79 Stat. 27.

[9] *See, e.g.*, Religious Land Use and Institutionalized Persons Act of 2001, Pub. L. 106-274, 114 Stat. 803 (2000).

for a "congressional negative" on state laws. However, to observe that the negative's opponents "viewed it as unnecessary once the Supremacy Clause had been included in the Constitution," *id.* at 17, is hardly to establish that the Supremacy Clause was meant to have an equally sweeping effect on state law. If anything, the Framers' rejection of the negative ought to cast doubt on the assertion that a federal administrative agency can effectively "negative" state law simply by promulgating a preamble in an interpretive regulation.

Petitioner's *amici*'s more substantial argument against the *Rice* presumption rests on an incomplete reading of an article by Professor Caleb Nelson. *See* Caleb Nelson, *Preemption*, 86 VA. L. REV. 225 (2000); *see* Br. of *Amicus Curiae* Product Liability Advisory Council, Inc., in Support of Petr. ("PLAC Brief"), at 13-15; Chamber Brief at 13-14, 18.[10] We respectfully disagree with some of Professor Nelson's conclusions, but we note that his conclusions, considered in their entirety, actually support Respondent's position in this case.

The Supremacy Clause provides that the Constitution, treaties, and federal statutes "shall be the supreme Law of the Land; and the Judges in every State shall be bound thereby, any Thing in the Constitution or Laws of any State to the Contrary notwithstanding." U.S. CONST. ART. VI, cl. 2. Professor Nelson argues that the last phrase would have been understood by the Founding generation as a "*non obstante* clause," which were frequently

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[10] The other scholars cited in the Chamber's brief rely, to varying degrees, on Professor Nelson.

employed to overcome the ordinary presumption against implied repeals of prior law. Nelson, *supra*, at 237-44. He argues that *Rice*'s presumption against preemption is inconsistent with this understanding: "A general rule that express preemption clauses should be read 'narrowly,' . . . . is hard to square with the Supremacy Clause's *non obstante* provision." *Id.* at 293.

Professor Nelson notes that "[o]ne should not take this point too far," *id.* at 294, and he has no quarrel with the proposition that "judges should generally be 'reluctant to infer pre-emption.'" *Id.* at 293 (quoting *Exxon Corp. v. Governor of Md.*, 437 U.S. 117, 132 (1978)).[11] It seems fair to read Professor Nelson's argument as foreclosing only a presumption that would be far more rigid than the way this Court has traditionally applied *Rice*.[12] Moreover, as the language quoted above indicates, his argument is limited to *express* preemption cases. *See also id.* at 292. His originalist reading of the Supremacy Clause has quite different implications for cases of *conflict* preemption such as this one.

According to Professor Nelson, "the Supremacy Clause puts the doctrine of preemption within the same general framework as the traditional doctrine

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[11] The PLAC Brief's suggestion that Professor Nelson's research supports "a presumption *in favor* of preemption," PLAC Brief at 15, thus misrepresents his actual conclusions.

[12] Professor Nelson also acknowledges that, given the placement of the semicolon in the Supremacy Clause, "the *non obstante* provision might have been directed especially at state judges," *id.* at 260—not at this Court. *But see id.* at 258-59 (arguing that the Framers played fast and loose with punctuation).

of repeals," *id.* at 245-46, which held that a later law superseded an earlier one only where the two provisions were "repugnant" to one another, *id.* at 236 (quoting 1 William Blackstone, *Commentaries* 59 (1765)). The Supremacy Clause established a rule of *federal* priority rather than a temporal one, but "the Supremacy Clause's rule of priority matters only when state law is 'repugnant to' valid federal law; the rule of priority comes into play only when courts cannot apply *both* state law *and* federal law, but instead must choose between them." *Id.* at 251. Under this "logical-contradiction test," *id.* at 260, broad notions of "obstacle preemption" are unconstitutional, *see id.* at 265-90. "[C]ourts could no longer find preemption simply because they think that state law hinders accomplishment of the 'full purposes and objectives' behind a federal statute." *Id.* at 304.

It is understandable that Petitioner's *amici* do not invoke this latter aspect of Professor Nelson's argument—it would eviscerate their argument for conflict preemption in this and many other cases. But his anti-obstacle preemption conclusion is inextricable from his attack on the *Rice* presumption, upon which petitioner's *amici* do rely:

> To be sure, [the *Rice*] presumption makes some sense within the Framework that the Supreme Court has developed for preemption cases . . . . By telling judges to approach federal statutes with "the starting presumption that Congress does not intend to supplant state law," the Supreme Court offsets its own expansive formulations of

> "implied" preemption. The presumption thus operates as an artificial way to bring the courts' results closer to Congress's probable "pre-emptive intent." Still, the presumption is a second-best alternative to a broader overhaul of the Court's doctrine.

Id. at 290-91. If this Court accepts Nelson's invitation to reconsider the *Rice* presumption, it should also reconsider the breadth of its conflict preemption jurisprudence. Nelson's historical research provides no support, however, for doing one without the other.

Even if we take the *non obstante* argument in isolation, it is limited to overcoming the traditional canon disfavoring implied repeals. As the preceding section makes clear, however, the *Rice* presumption rests not on the implied repeals canon but rather on the evolving structure of our federalism. The presumption developed in response to the expanding scope of potential federal regulatory authority in the mid-20th century, which transformed our federalism from a regime of separate spheres to one of concurrent powers. And the presumption responds to the parallel shift from relatively vigorous judicial enforcement of constitutional boundaries to a primary reliance on political and procedural checks on national authority. Professor Nelson acknowledges that "[w]hile the *non obstante* provision tells courts not to apply the general presumption against implied repeals in preemption cases, it does not require them to discard their other tools of statutory interpretation." *Id.* at 294. This Court's federalism-based "clear statement" rules and

presumption against preemption, which developed long after the period examined by Professor Nelson, are among those "other tools". It makes little sense to apply a contemporary sense of the scope of Congress's regulatory authority but insist on a *circa* 1789 set of preemption rules.

C. The *Rice* Presumption Applies to Cases of Implied Conflict Preemption.

Petitioner's *amici* also contend that the *Rice* presumption "is simply inapplicable to cases involving conflict preemption." Chamber Brief at 27; *see also* PLAC Brief at 15-19. We are at a loss to understand why courts should be *less* willing to find preemption when Congress has addressed the matter directly than in conflict cases, where Congress has not articulated its preemptive intent. This would turn the whole point of the *Rice* presumption—to ensure that the States' representatives in Congress consider and resolve questions of preemption themselves—on its head. Unsurprisingly, this Court has never endorsed the proposition advanced by Petitioner's *amici*.

Any confusion concerning the application of *Rice* in conflict cases stems from a belief that conflict cases focus only on the functional interplay of state and federal law. But that is an incomplete description of what courts do in cases involving conflict preemption. As this Court has made clear, the basic inquiry in *all* preemption cases—including conflict cases—concerns the intent of Congress. *See, e.g.*, *Medtronic*, 518 U.S. at 485 ("'[t]he purpose of Congress is the ultimate touchstone' in every pre-emption case."). The *Rice* presumption helps divine this intent.

In some cases it will be quite difficult to distinguish interpreting a statute's *express* preemptive effect from determining its purpose and effect for conflict purposes. *See Gade v. Nat'l Solid Wastes Mgmt. Ass'n*, 505 U.S. 88, 104 n.2 (1992) (plurality opinion) ("[O]ur pre-emption categories are not 'rigidly distinct'") (quoting *English v. Gen. Elec. Co.*, 496 U.S. 72, 79, n.5 (1990)). It thus makes little sense to have different interpretive rules for conflict and express preemption. To take one obvious example, Section 636 of the federal Cable Act expressly preempts state law that is "inconsistent with this Act." 47 U.S.C. § 556(c). State law is *expressly* preempted, in other words, if it *conflicts* with federal law. Which interpretive rule would Petitioner's *amici* apply to a statute like this one? Putting this sort of conundrum aside, there are any number of cases in which the justices of this Court have disagreed as to whether the preemption at issue is best described as express or conflict preemption. *Compare, e.g.*, *Gade*, 505 U.S. at 103 n.2 ("We cannot agree that the negative implications of the text, although ultimately dispositive to our own *analysis*, *expressly* address the issue of federal pre-emption of state law. We therefore prefer to place this case in the category of implied pre-emption."), *with id.* at 111-12 (Kennedy, J., concurring in the judgment) (arguing that the preemption at issue was better characterized as express).

The present case demonstrates two perennial interpretive issues that arise across a variety of conflict preemption cases, and the *Rice* presumption sheds helpful light on each. The first issue involves identifying the relevant statutory purposes. If

Congress has but a single purpose in enacting a law, then state regulation that goes further in pursuit of that purpose most likely will not conflict with Congress's intent. Congress frequently has multiple purposes, however, and those purposes will almost always trade off with one another to some extent. In this case, for example, Congress's purposes include both ensuring the safety of drugs and promoting their availability. In such circumstances, opponents of state regulation can *always* claim that Congress has struck a balance between these purposes, so that *any* additional state regulation will disrupt the federal regulatory equilibrium.

This generic form of the argument, however, proves too much. Instead, the courts must interpret the regulatory scheme to determine whether Congress really meant to lock in a specific balance among competing purposes, or whether Congress intended to permit state variation within some reasonable range so long as state law furthered the primary purpose of the federal scheme. The *Rice* presumption is as helpful a default in these circumstances as it is with respect to express preemption clauses. It suggests that federal legislation should rarely be construed to represent a fixed balance among competing purposes that excludes state variation. *See, e.g.*, *Gade*, 505 U.S. at 111 (Kennedy, J., concurring in the judgment) ("A free wheeling judicial inquiry into whether a state statute is in tension with federal objectives would undercut the principle that it is Congress rather than the courts that pre-empts state law.").

The second issue concerns the effect of a federal *ex ante* approval of a product on *ex post* state

regulation, frequently through the tort system. We take up the merits of this issue with respect to drugs in Part II, *infra*. Here, we simply note that this sort of issue requires a careful analysis of what Congress intended the federal approval process to accomplish, the extent of federal *ex post* safeguards built into the scheme and whether Congress intended those safeguards to be exclusive, and what concerns—if any—it meant to leave to state *ex post* regulation. Again, no incongruity arises from applying a default rule like the *Rice* presumption to resolve ambiguities in Congress' intent concerning these matters.

Not surprisingly, this Court has had little trouble applying *Rice* to claims of conflict preemption. In *Rush Prudential HMO, Inc. v. Moran*, 536 U.S. 355, 387 (2002), for example, this Court applied the presumption against preemption to reject a claim that state law conferred remedies on HMO participants that were inconsistent with ERISA's remedial scheme.[13] Likewise, this Court has applied a presumption against preemption under the National Labor Relations Act, even though "[t]he NLRA contains no express pre-emption provision." *Bldg. & Constr. Trades Council v. Associated Builders & Contractors of Mass./R. of the Metropolitan Dist. I., Inc.*, 507 U.S. 218, 224 (1993). And in *California v. ARC America Corp.*, 490 U.S. 93, 101-102 (1989), this Court invoked *Rice* in the course of rejecting an obstacle preemption claim under the

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[13] The dissent made clear that the preemption claim relied on "ordinary principles of conflict pre-emption." 536 U.S. at 401 (Thomas, J., dissenting).

federal antitrust laws.[14] There is simply no basis, in either logic or experience, for holding the presumption against preemption inapplicable to conflict cases.

II. FDA Approval of a Drug Does Not Preempt Supplementary State Regulation.

The effect of federal agency approvals of products and practices is a recurring issue, but that does not mean that all such approvals should be treated the same. This Court has held, for example, that premarket approval of medical devices by the FDA preempts state common law claims challenging the safety and effectiveness of such devices, *see Riegel v. Medtronic, Inc.*, 128 S. Ct. 999 (2008), but it has refused such effect to the FDA's "substantial equivalence" approvals of such devices, *see Medtronic, Inc. v Lohr*, 518 U.S. 470 (1996). We argue in this Part that the FDA's premarket approval of a *drug* should not have preemptive effect for three reasons: First, the statutory regime for drugs lacks the explicit preemption provision enacted by

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[14] *See also Pharm. Research and Mfrs. of America v. Walsh*, 538 U.S. 644, 666 (2003) (plurality opinion) (applying the *Rice* presumption to a conflict claim under the Medicaid statute); *accord id.* at 681 n.4, 682 (Thomas, J., concurring in the judgment) (same); *Ca. Fed. Sav. & Loan Ass'n v. Guerra*, 479 U.S. 272, 281, 288 (1987) (applying a presumption against preemption in the course of rejecting a claim that a state pregnancy discrimination statute conflicted with Title VII); *Hillsborough Cty., Fla. v. Automated Med. Laboratories, Inc.*, 471 U.S. 707, 716 (1985) ("Appellee must thus present a showing . . . of a conflict between a particular local provision and the federal scheme, that is strong enough to overcome the presumption that state and local regulation of health and safety matters can constitutionally coexist with federal regulation.").

Congress for devices and applied by this Court in *Riegel*. Second, *ex post* regulation by the state tort system provides a necessary supplement to FDA postapproval review of drug safety, in light of crucial limitations on FDA resources and data-gathering authority. Third, the FDA's recent policy reversal according new preemptive effects to its drug approvals is entitled to little, if any, deference from the courts.

A. Congress Has Conspicuously Declined to Preempt State Claims Concerning Drugs.

Although this Court's decision in *Riegel* seems to have posed a similar question to this case, Congress has made clear that the regulation of drugs is to be treated differently from that of medical devices under the FDCA. The MDA contains an express preemption provision: "no State . . . may establish or continue in effect with respect to a device intended for human use any requirement—(1) which is different from, or in addition to, any requirement applicable under this chapter to the device; and (2) which relates to the safety or effectiveness of the device or to any other matter included in a requirement applicable to the device under this chapter." 21 U.S.C. §360k(a). *Riegel* held that this provision preempted a state tort action, but the Court acknowledged that "Congress could have applied the pre-emption clause to the entire FDCA. It did not do so, but instead wrote a pre-emption clause that applies only to medical devices," 128 S. Ct. at 1009.

There is no corresponding express preemption provision for drug approval under the FDCA. Congress has amended the FDCA numerous times

without adding any preemption clause, and state common law claims remain an important part of the regulatory scheme.[15]

Congress rejected a proposal to include a right of action for damages in the 1938 FCDA because "a common law right of action exists." *Hearing Before a Subcomm. of the Comm. on Commerce of the U.S. Senate on S. 1944*, 73d Cong. 2d Sess. 400, 403 (1933). And in the 1962 amendments, Congress even included a savings clause: "Nothing in the amendments made by this Act . . . shall be construed as invalidating any provision of State law which would be valid in the absence of such amendments unless there is a direct and positive conflict between such amendments and such provision of State law." Pub. L. No. 87-781, §202, 76 Stat. 780, 793 (1962). Congress amended the FDCA again recently with the Food & Drug Administration Amendments Act of 2007 (FDAAA), and again chose not to enact a generally applicable express preemption provision, despite efforts by the pharmaceutical industry to obtain such a provision. *See* Pub. L. No. 110-85, 121 Stat. 823 (2007); David A. Kessler & David C. Vladeck, *A Critical Examination of the FDA's Efforts to Preempt Failure-to-Warn Claims*, 96 GEO. L.J. 461, 468 & n. 27 (2008) (noting the disappointment of counsel for the pharmaceutical industry) (hereinafter, "Kessler & Vladeck"). The absence of

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[15] This refusal to add a preemption provision to the statute governing drug regulation has taken place even as Congress has added preemption provisions to at least 27 laws since 2001. *See* U.S. HOUSE OF REPS. COMM. ON GOV'T REFORM – MINORITY STAFF, SPECIAL INVESTIGATIONS DIVISION, CONGRESSIONAL PREEMPTION OF STATE LAWS AND REGULATIONS, 1, 17-38 (2006).

such a provision in the FDAAA is not mere oversight on the part of Congress—the legislative record indicates that preemption implications were considered by Congress,[16] and, ultimately, Congress decided to expressly preempt only a very narrow category of state regulation. *See* Pub. L. 110-85, Title VIII, § 282(d), 121 Stat. 922 (Sept. 27, 2007) (preempting state registering requirements for certain clinical trials).

Nor has Congress granted the FDA authority to unilaterally alter the preemptive effect of its drug labeling regulation. The MDA expressly preempts "different" or "addition[al]" state law requirements and delegates to the FDA a specific role in determining the Act's preemptive reach, but nothing in the FDCA indicates that Congress intended FDA drug labeling regulation to have equivalent effect. Nor is there any provision conferring authority on FDA to make a determination as to when consistent but different or additional state requirements would be preempted. *Compare* 21 U.S.C. § 360k *with* 21 U.S.C. § 301, *et seq.*; *see also Medtronic*, 518 U.S. at 495-496 (discussing the FDA's unique role in determining the scope of § 360k's pre-emptive effect).

The stark textual disparity between this case and *Riegel* ought to require a different result. This Court has noted that "[t]he case for federal pre-emption is particularly weak where Congress has indicated its awareness of the operation of state law in a field of federal interest, and has nonetheless decided to 'stand by both concepts and to tolerate

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[16] *See* fn. 21 and accompanying text, *infra*.

whatever tension there [is] between them.'" *Bonito Boats, Inc. v. Thunder Craft Boats, Inc.*, 489 U.S. 141, 166-67 (1989) (quoting *Silkwood v. Kerr-McGee Corp.*, 464 U.S. 238, 256 (1984)).[17] Petitioner's effort to achieve the same result as the MDA's express preemption clause on *conflict* preemption grounds in drug cases invites this Court to substitute its own policy judgment for that of Congress.

In any event, it is not difficult to postulate sound reasons why Congress treated drugs differently from devices. As the *Riegel* Court noted, the MDA was spurred by several states' adoption of premarket approval regimes in the wake of the Dalkon Shield failure. 128 S. Ct. at 1002. Although *Riegel* held that the textual sweep of the MDA's preemption clause encompassed common law claims as well, there is no dispute that state premarket regimes were the primary object of Congress's preemptive intent. *See also Medtronic*, 518 U.S. at 489 ("[W]hen Congress enacted §360k, it was primarily concerned with the problem of specific, conflicting state statutes rather than the general duties enforced by common actions."). Throughout the development of the FDCA's regime for drugs, by contrast, "no state regulations required premarket approval of the drugs or additives in question, so no preemption clause was needed as a check against potentially conflicting state regulatory regimes."

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[17] *See also Bates v. Dow Agrosciences LLC*, 544 U.S. 431, 449-450 (2005) ("The long history of tort litigation against manufacturers of poisonous substances adds force to the basic presumption against pre-emption. If Congress had intended to deprive injured parties of a long available form of compensation, it surely would have expressed that intent more clearly.").

Riegal, 128 S. Ct. at 1018 (Ginsburg, J., dissenting). The omission of an express preemption clause for drugs was thus no mere oversight, but rather a considered judgment that state law did not pose a threat to the federal regulatory regime in that area.

Moreover, the choice to preempt state common law regulation turns, at least in part, on the confidence that Congress has in the FDA's own capacity to monitor drug safety after drugs are approved and marketed. As the next section demonstrates, Congress had good reason to doubt that capacity in the case of drugs.

B. State Tort Litigation Provides a Valuable and Necessary Supplement to FDA Review.

As Judge Calabresi recently noted, the issues in this case implicates the "considerable and undisputed" power of the states to protect consumers. *Desiano v. Warner-Lambert & Co.*, 467 F.3d 85, 86 (2nd Cir. 2006), *aff'd by an equally divided court*, 128 S. Ct. 1168 (2008). Prior to 2002, the FDA's position was that FDA approval and state tort liability operate independently, "each providing a significant, yet distinct, layer of consumer protection." Margaret Jane Porter, *The* Lohr *Decision: FDA Perspective and Position*, 52 FOOD & DRUG L.J. 7, 11 (1997) (written by then chief counsel for the FDA) (hereinafter, Porter).[18] This shared authority, favored by the FDA

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[18] *See also* 63 Fed. Reg. 66378, 66384 (Dec. 1, 1998) ("FDA's regulations establish the minimum standards necessary, but were not intended to preclude the states from imposing additional labeling standards.").

for nearly a century, allows state law to compensate for limits on the FDA's resources, offset the potential for agency capture, provide a monitoring system for those risks not anticipated at the time of FDA approval, react quickly to address such unanticipated dangers, and compensate injured parties.

The FDA's policy reversal occurred in the teeth of rising concerns about the FDA's oversight of drug safety. These concerns go both to the comprehensiveness of premarket trials and the FDA's capacity to conduct adequate postmarketing monitoring of drug safety. "Even if it is rigorously conducted, a process that focuses on prior approval inevitably will fail to capture all relevant information." Catherine T. Struve, *The FDA and the Tort System: Postmarketing Surveillance, Compensation, and the Role of Litigation*, 5 YALE J. HEALTH POL'Y L. & ETHICS 587, 598 (2005). Premarket trials often do not reveal all of the potential risks posed by a drug; as a recent study by the National Academies' Institute of Medicine concluded, "[t]he approval decision does not represent a singular moment of clarity about risks and benefits associated with a drug." Inst. of Med. of the Nat'l Acads., THE FUTURE OF DRUG SAFETY: PROMOTING AND PROTECTING THE HEALTH OF THE PUBLIC 27 (Alina Baciu, Kathleen Stratton & Shelia P. Burke eds., 2006) ("IOM Study"). This is particularly true when drug risks relate to "vulnerable populations," involve interaction with other medications, do not manifest for an extended period of time, or are rare among the general population (though perhaps common among a particular subset of the population). *See* IOM Study at 37-38. In fact,

growing evidence reveals that some pharmaceutical manufacturers have designed their premarket trials in ways that are more likely to produce favorable results; that some manufacturers have reported data from premarket trials to the FDA selectively or interpreted them in ways more favorable to their interests; and that the FDA's oversight process does not always catch these errors. *See, e.g.*, Thomas O. McGarity & Wendy E. Wagner, BENDING SCIENCE: HOW SPECIAL INTERESTS CORRUPT PUBLIC HEALTH RESEARCH 60-76, 85-87, 183-89, 246-51 (2008).

Because of these limitations on premarket analysis, the FDA has mechanisms in place for postmarket monitoring of drugs. But a recent Government Accountability Office study concluded that the "FDA lacks a clear and effective process for making decisions about, and providing management oversight of, postmarket drug safety issues. The process has been limited by a lack of clarity about how decisions are made and about organizational roles, insufficient oversight by management, and data constraints." Government Accountability Office, DRUG SAFETY: IMPROVEMENT NEEDED IN FDA'S POSTMARKET DECISION-MAKING AND OVERSIGHT PROCESSES 5 (March 2006) ("GAO Report"); Kessler & Vladeck, *supra*, at 470. Likewise, the Institute of Medicine study concluded that the FDA lacks the resources needed to accomplish its goals and that the obstacles to accomplishing those goals will only increase in the future. IOM Study at 36. As another report explains, "[t]he majority of FDA program resources are devoted to premarketing scientific risk identification and assessment and approval or nonapproval. Significant, but substantially fewer,

resources are devoted to postmarketing surveillance and risk assessment activities." U.S. Dep't of Health & Human Servs. (HHS), REPORT TO THE FDA COMMISSIONER FROM THE TASK FORCE ON RISK MANAGEMENT: MANAGING THE RISKS FROM MEDICAL PRODUCT USE – CREATING A RISK MANAGEMENT FRAMEWORK 30 (1999) (hereinafter, "HSS Report").[19] A recent internal survey of FDA reviewers in the Center for Drug Evaluation and Research (CDER) found that "some two-thirds of respondents were either '[n]ot at all confident' or only '[s]omewhat confident' that the CDER 'adequately monitors the safety of prescription drugs once they are on the market." Struve, *supra*, at 601 (citing Office of Inspector General, HSS, HHS Survey at question 45).

Much of the FDA's postapproval surveillance is accomplished through review of adverse event reporting; however, postmarketing reporting suffers from both underreporting and overreporting. Only a small fraction of adverse reactions are reported. *See Reauthorization of the Prescription Drug User Fee Act: Hearing Before the Subcomm. on Health of the H. Comm. on Energy and Commerce*, 107th Cong. 49 (2002) (Rep. Waxman); Phil B. Fontanarosa, M.D., *et al.*, *Postmarketing Surveillance – Lack of Vigilance, Lack of Trust*, 292 J. AM. MED. ASS'N 2647, 2647 (2004). Despite this, postmarketing adverse event reporting overwhelms the FDA's ability to digest the information provided. *See* HHS Report at 58 (likening the FDA's system for managing the

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[19] Although the FDAAA increases the resources available to the FDA for postapproval surveillance, it also significantly increases the postapproval responsibilities that draw on those resources.

information to searching for the proverbial needle in the haystack).

Recent and well-publicized examples highlight the FDA's inability to single-handedly police the labeling of drugs after those drugs reach the market. In May of 1999, the FDA approved Vioxx for the treatment of arthritis pain. Although the preapproval studies did not show any increased risk of heart attack, Merck submitted data to the FDA in June of the following year disclosing a significant increased risk of heart attack in Vioxx users. The FDA did not approve a new warning relating to the increased cardiovascular risks associated with Vioxx until April of 2002, however, and did not initiate its own study of these risks until 2003. *See* the FDA's "Vioxx Questions and Answers" page, available at http://www.fda.gov/cder/drug/infopage/vioxx/vioxxQA.htm. Merck later withdrew Vioxx from the market after a second clinical trial confirmed the first and demonstrated a two-fold increase in risk of heart attack. The FDA's failure to take stronger and swifter action has been widely criticized.

Congress took steps to improve postmarketing monitoring of drug safety in the FDAAA in 2007. The new amendments expanded the FDA's authority to mandate postmarketing safety studies; however, the studies that the FDA was able to persuade drug companies to undertake under the former regime were generally not completed, and it is unclear if the new statute will improve on that record. *See* HHS, FDA, Report on the Performance of Drug and Biologics Firms in Conducting Postmarketing Commitment Studies; Availability, 73 Fed. Reg. 22157, 22158 (April 24, 2008) (as of September 2007,

71% of postmarketing study commitments for approved new drugs had not yet been started even though nearly half of those commitments were more than three years old; only 26% of outstanding postmarketing study commitments were either completed or proceeding on schedule).[20] Congress seems to have lacked confidence that the new amendments would obviate the need for state tort law. Not only did Congress eschew an MDA-like express preemption clause, but the FDAAA's expansion of FDA authority to mandate postmarketing labeling changes included a "Rule of Construction" stating that nothing therein affects the responsibility of manufacturers to "maintain its label in accordance with existing requirements, including subpart B of part 201 and sections 314.70 and 601.12 of title 21, Code of Federal Regulations (or any successor regulations)." 21 U.S.C. §355(o)(4)(I). The CFR sections specifically mentioned are the basis for a manufacturer's ability to change drug labeling when appropriate without prior approval from the FDA through the Changes Being Effected (CBE) process—the authority, in other words, that Respondent argues permits drug manufacturers to adjust their label in response to state tort rulings. Br. of Respt. at 37-43. The FDAAA's Rule of Construction thus accommodates the operation of state tort obligations.[21]

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[20] HHS, Office of Inspector General, *FDA's Monitoring of Postmarketing Study Commitments*, 8, 11-12 (June 2006) (noting sporadic compliance with postmarketing commitments).

[21] *See* 153 Cong. Rec. S11832, col. 3, S11833, cols. 1-2 (Sept. 20, 2007) (Sen. Kennedy); *id.* at S11834, cols. 2-3 (Sen. Leahy); *id.* at S11835, col. 3 (Sen. Durbin).

As the FDAAA suggests, the relationship between the FDA and state litigation in the context of policing drug labeling is symbiotic.[22] The FDA has an expertise and big-picture vantage point that juries may not possess; state litigation, on the other hand, serves a number of functions that the FDA is not well-suited to perform. For example, litigation provides an incentive for manufactures to monitor actively and remediate quickly any new or increased dangers posed by approved drugs. State tort litigation frequently unveils and highlights important but previously undisclosed information. *See* Aaron S. Kesselheim, M.D., J.D. & Jerry Avorn, M.D., *The Role of Litigation in Defining Drug Risks*, 297 J. OF AM. MED. ASS'N 308, 308-309 (2007) (collecting examples); *see also Bates*, 544 U.S. at 451 (noting a similar dynamic with respect to pesticide regulation). And litigation provides the sole source of compensation for parties injured by inadequately or improperly labeled drugs. *See* Thomas O. McGarity, THE PREEMPTION WAR 233 (forthcoming 2008) (tort verdicts spread risk among beneficiaries of a product such that, when risk-benefit analysis mandates the acceptance of certain risk at the agency level, the costs of that risk are spread among those who benefit from the product rather than being born solely by the unlucky victims).[23]

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[22] *See* William W. Buzbee, *Asymmetrical Regulation: Risk, Preemption, and the Floor/Ceiling Distinction*, 82 N.Y.U. L. REV. 1574, 1585 (2007) ("[T]he different actors and modalities of state common law litigation make it a critical, although only partial, antidote to predictable sorts of government failures.").

[23] Much skepticism of state tort law stems from concerns about lay juries. The evidence driving such concerns is generally

Developments in the drug approval process have increased the importance of state common law in drawing attention to the risks posed by marketed drugs and compensating victims of the failure to adequately disclose such risks. Drugs were historically approved in Europe before they were made available in the U.S., but new drugs are now most often approved and marketed in the U.S. before they have been vetted anywhere else in the world. *See* Kessler & Vladeck, *supra,* at 486. At the same time, drug recalls and withdrawals in the U.S. have been increasing. *See* GAO, FOOD AND DRUG ADMINISTRATION: EFFECT OF USER FEES ON DRUG APPROVAL TIMES, WITHDRAWALS, AND OTHER AGENCY ACTIVITIES 4 (2002). As the editors of the *New England Journal of Medicine* recently concluded, "[p]reemption will undermine the confidence that doctors and patients have in the safety of drugs and devices." Gregory D. Curfman, Stephen Morrissey, & Jeffrey M. Drazen, *Why Doctors Should Worry about Preemption*, N. ENG. J. MED., July 3, 2008, at 3.

C. The FDA's "Preemption Preamble" Warrants Little or No Deference.

This Court has been reluctant to decide the precise level of deference, if any, that courts owe to an agency's determination that the statute it enforces preempts state law. We believe that, as a general matter, deference to an agency's preemptive

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anecdotal: empirical work on jury verdicts in medical malpractice cases, by contrast, shows that jury verdicts reach comparable results to the judgments of medical professionals. *See* Neil Vidmar & Valerie P. Hans, AMERICAN JURIES: THE VERDICT, 188-89, 327-31 (2007).

interpretation of an ambiguous statute is inconsistent with the *Rice* presumption; moreover, federal agencies deciding preemption issues generally lack the comparative institutional competence advantages that they may enjoy with respect to other, more policy-oriented questions. *See generally,* Ernest A. Young, *Executive Preemption*, 102 NW. U. L. REV. 869, 883-89 (2008). In any event, the particular agency action at issue here—the FDA's so-called "preemption preamble"—is unworthy of deference under ordinary principles of administrative law.

1. Preemption is an inappropriate subject for deference generally.

The issue of deference to agency interpretation of statutes arises only when the underlying statute is ambiguous. In preemption cases, however, such ambiguity triggers the *Rice* presumption against preemption. This Court has never resolved the tension between its preemption jurisprudence and notions of administrative deference.[24] Most of the cases in which the Court has deferred to agencies on preemption questions involved agency findings of *no* preemption. *See, e.g., Sprietsma v. Mercury Marine*, 537 U.S. 51, 68-70 (2002); *Medtronic, Inc. v. Lohr*, 518 U.S. 470, 495-96 (1996); *Hillsborough County,*

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[24] *Watters v. Wachovia Bank, N.A.*, 127 S. Ct. 1559, 1584 (2007) (Stevens., J., dissenting) ("[W]hen an agency purports to decide the scope of federal preemption, a healthy respect for state sovereignty calls for something less than *Chevron* deference."); *Medtronic*, 518 U.S. at 512 (O'Connor, J., concurring in part and dissenting in part) ("It is not certain that an agency regulation determining the pre-emptive effect of *any* federal statute is entitled to deference[.]").

Fla. v. Automated Med. Laboratories, Inc., 471 U.S. 707, 716-18 (1985). In such cases, the tension with *Rice* does not arise. In *Geier v. Am. Honda Motor Co.*, 529 U.S. 861, 883 (2000), the Court did accord "some weight" to an agency's determination that state law was preempted, but it has never suggested that anything more than *Skidmore* deference, at most, is appropriate.

Courts should be particularly wary of deferring to an agency's determination of the preemptive effects of its regulations or governing statutes. Federal agencies do not represent the states, and their interests do not always align. *See, e.g.* Letter from Steven Rauschenberger, president, National Conf. of State Legis. to Michael Leavitt, secretary of HHS (Jan. 13, 2006) (complaining that the FDA's preemption preamble shows a "complete disregard for our dual system of government"). Indeed, agencies are notoriously unwilling to consider federalism values even where standing executive orders require them to do so. *See* Nina A. Mendelson, Chevron *and Preemption*, 102 MICH. L. REV. 737, 783 (2004) ("In 1999, the General Accounting Office reported that only five federalism impact statements had been prepared for the over 11,000 final rules agencies issued between April 1996 and December 1998.").

It is true, of course, that agency expertise will be valuable with respect to certain aspects of the preemption decision. But agencies have little comparative advantage with respect to the basic task of statutory construction. Preemption determinations require interpretations of both federal *and state* law, moreover, and federal agencies have no expertise with respect to the latter. *See*

Thomas W. Merrill, *Preemption and Institutional Choice*, 102 NW. U. L. REV. 727, 758 (2008) (hereinafter, "Merrill"). Likewise, a federal scientist's assessment of the likelihood of jury error in tort litigation is unlikely to be any better informed than that of the average layperson.

Deference to agency preemption determinations, moreover, makes the agency judge in its own case. Courts have long worried about trusting agencies to determine the scope of their own jurisdiction.[25] *See* Timothy K. Armstrong, Chevron *Deference and Agency Self-Interest*, 13 CORNELL J.L. & PUB. POL'Y 203, 209-11 (2004); Ernest Gellhorn & Paul Verkuil, *Controlling* Chevron*-Based Delegations*, 20 CARDOZO L. REV. 989, 992-94 (1999). The tendencies toward empire building and agency capture inherent in agencies are exacerbated by the ability to expand one's own power through preemption. *See* Merrill, *supra*, at 756; Buzbee, *supra*, at 1590 (identifying agencies' incentive to make themselves the sole locus of regulatory choice).

It is particularly ironic that Petitioner's *amici*, who begin by recounting the Philadelphia Convention's rejection of a congressional negative over state laws, end up endorsing an *executive* negative in the form of broad powers of agency preemption. To the extent that any "law that ought to be negatived will be set aside in the Judiciary department," 2 FARRAND'S RECORDS 28, this Court should make its preemption determination without

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[25] "No man is allowed to be a judge in his own cause; because his interest would certainly bias his judgment, and, not improbably, corrupt his integrity." THE FEDERALIST NO. 10 (James Madison).

undue deference to the agency's own self-serving views.

2. The FDA's "preemption preamble" lacks the indicia of deliberation, consistency, and persuasiveness necessary for deference.

The FDA's "preemption preamble" is not entitled to *Chevron* deference because it was not promulgated in the exercise of delegated authority to act with the force of law. *See, e.g.*, *U.S. v. Mead Corp.*, 533 U.S. 218, 229 (2001); *Christensen v. Harris County*, 529 U.S. 576, 586-87 (2000). Nor was the preemption preamble submitted for notice and comment; indeed, the initial notice of intent to revise the regulations affirmatively stated that the regulations would not preempt state tort claims. *See* Requirements on Content and Format of Labeling for Prescription Drugs and Biologics; Requirements for Prescription Drug Product Labels, 65 Fed. Reg. 81082, 81103 (Dec. 22, 2000).[26]

Under *Mead*, the bases for deference to an agency decision include the formality, consistency, thoroughness, and persuasiveness of the agency's

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[26] *See also* David C. Vladeck, *The FDA and Deference Lost: A Self-Inflicted Wound or the Product of a Wounded Agency? A Response to Professor O'Reilly*, 93 CORNELL L. REV. 981, 991 (2008) ("In the past, the FDA generally submitted its decisions on preemption policy to the rulemaking process, thereby subjecting the decision to public comment and ultimately to judicial review. The FDA is also required by Executive Order to give state and local governments notice and an opportunity to participate in any proceeding that may affect state or local law. The FDA did none of this with its new preemption position.").

view. *Mead*, 533 U.S. at 228. The FDA's preemption preamble is lacking in all of these dimensions. As noted above, the preemption preamble was adopted without a formal process and following statements by the FDA that the rules at issue would not preempt state tort actions. The FDA thus acted without receiving all expertise available on the issue.

Likewise, the FDA's preamble is inconsistent with its previous stance. For years previously, the FDA's considered judgment had been that state tort law is complementary to FDA drug regulation. *See, e.g.*, 63 Fed. Reg. 66378, 66384 (Dec. 1, 1998) ("FDA's regulations establish the minimum standards necessary, but were not intended to preclude the states from imposing additional labeling standards."); *see also* Porter, *supra*, at 11 ("The most important theme of this article is that the agency's position in *Lohr* and the Court's decision are the logical extensions of the agency's long-standing presumption against preemption in implementing section 521 of the [FDCA]."). In the absence of any explanation regarding how that change is grounded in changes in the industry, the new policy cannot be considered an instance of expert judgment. *Cf. Bates*, 544 U.S. at 449 (considering an agency's preemptive conclusion "particularly dubious" in light of its recent change in position).

The FDA's position also lacks persuasiveness because Congress knew of the FDA's consistent position that state tort laws were not preempted and took no action to change this treatment. State tort damage suits existed even before Congress passed the original FDCA in 1938. *See, e.g., Halloran v. Parke, Davis & Co.*, 245 A.D.727, 280 N.Y.S. 58

(1935); *Thomas v. Winchester*, 6 N.Y. 397 (1852). Yet, as described above, Congress has consistently refused to add a preemption provision concerning drug regulation to the FDCA.

This case is thus somewhat analogous to *FDA v. Brown & Williamson Tobacco Corp.*, 529 U.S. 120 (2000). In *Brown & Williamson*, the FDA had asserted jurisdiction over regulation of tobacco products after consistently stating that it had no such jurisdiction. One factor supporting the Court's conclusion that the FDA lacked such jurisdiction was Congress's acceptance of this position in passing other tobacco-regulating legislation and rejecting proposed legislation that would explicitly have given the FDA jurisdiction over tobacco regulation. Although Congress did not in this case pass legislation specifically in reliance on the FDA position against preemption, it has similarly refused to pass legislation overriding the FDA's position. This is strong evidence that the FDA's prior position was consistent with the intent of Congress.

Conclusion

The decision of the Supreme Court of Vermont should be affirmed.

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IN THE

Supreme Court of the United States

WYETH,

Petitioner,

v.

DIANA LEVINE,

Respondent.

On Writ of Certiorari to the Supreme Court of Vermont

BRIEF FOR CONSUMERS UNION OF UNITED STATES, INC., AS *AMICUS CURIAE* IN SUPPORT OF RESPONDENT

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QUESTION PRESENTED

Whether Congress intended the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 301 *et seq.*, setting forth duties between drug manufacturers and regulator, to pre-empt drug manufacturers' independent duty of care and duty to warn consumers under state law.

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IN THE

Supreme Court of the United States

No. 06-1249

WYETH,

Petitioner,

v.

DIANA LEVINE,

Respondent.

On Writ of Certiorari to the Supreme Court of Vermont

BRIEF FOR CONSUMERS UNION OF UNITED STATES, INC., AS *AMICUS CURIAE* IN SUPPORT OF RESPONDENT

INTEREST OF *AMICUS CURIAE*[1]

Consumers Union of United States, Inc., publisher of *Consumer Reports*, is a nonprofit membership organization chartered in 1936 to provide consumers

[1] Pursuant to Rule 37.3(a) of the Rules of the Supreme Court of the United States, petitioner and respondent have lodged letters with the Court consenting generally to the filing of briefs *amicus curiae*, and accordingly, petitioner and respondent have consented to the filing of this brief. No counsel for a party in *Wyeth v. Levine*, Case No. 06-1249, authored this brief in whole or in part, and no person or entity other than *Amicus Curiae* Consumers Union, its members, or its counsel, made a monetary contribution to the preparation or submission of this brief. See Sup. Ct. R. 37.6.

with information, education, and counsel about goods, services, health and personal finance. Consumers Union's publications have a combined paid circulation of approximately 8.5 million. These publications regularly carry articles on Consumers Union's own product testing; on health, product safety, and marketplace economics; and on legislative, judicial, and regulatory actions that affect consumer welfare. Consumers Union's income is solely derived from the sale of *Consumer Reports*, its other publications and services, and noncommercial contributions, grants, and fees. Consumers Union's publications and services carry no outside advertising and receive no commercial support.

Consumers Union's mission is "to work for a fair, just, and safe marketplace for all consumers and to empower consumers to protect themselves." In line with that mission and our assessment of priorities, Consumers Union has actively worked for a fair and just marketplace for consumers in critical areas implicated by this case, including prescription drugs, drug advertising, health care, and patient safety. Consumers Union has filed actions in both state and federal courts in order to protect consumers, and has actively participated in a variety of proceedings before both state and federal regulatory agencies. For example, Consumers Union played an active role in securing the passage of the Federal Food, Drug, and Cosmetic Act of 1938 and the 1962 amendments to the Act. It has been extremely active in the area of testing, evaluating, and rating of prescription drugs and health services, in order to inform consumers and to advocate for consumers before Congress, state legislatures, and regulatory agencies. Consumers Union filed amicus briefs on pre-emption in *Med-*

tronic, Inc. v. Lohr, 518 U.S. 470 (1996), and in *Riegel v. Medtronic, Inc.*, 552 U.S. ___, 128 S. Ct. 999 (2008).

SUMMARY OF ARGUMENT

Petitioner Wyeth manufactured and sold Phenergan, a drug for the treatment of nausea. The drug manufacturer filed an application under the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 355(b), to sell the new drug in interstate commerce. After premarket review, the Food and Drug Administration approved the application in 1955. Jt. App., at 266-267; see also Pet. Br., at 11. The agency concluded that Wyeth's new drug met the minimum standards of safety for introduction into interstate commerce. 21 U.S.C. § 355(a).[2] Neither the Act nor the Food and Drug Administration's specific review and approval purported to repeal or pre-empt Wyeth's independent duties to its consumers under state tort law, namely its duty of care and its duty to warn.

In post-market experience, Phenergan has caused gangrene, resulting in amputation, when administered by certain intravenous injection. The premarket tests, application, review and approval did not disclose this grave danger, but it became apparent after post-market sales to consumers. See, e.g., Jt. App., at 268-269 (report of adverse reaction in 1965); *id.*, at 237, 240 (decision on motion for judgment, finding knowledge of danger "[s]ince at least 1976").

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[2] In 1955, section 355 required pre-market review and approval to assess general safety. Federal Food, Drug, and Cosmetic Act of 1938, Pub. L. No. 75-717, § 505, 52 Stat. 1040, 1052. In 1962, Congress added the requirement to assess general effectiveness. Drug Amendments of 1962, Pub. L. No. 87-781, § 102, 76 Stat. 780, 781.

After an intravenous injection of Phenergan in 2000, Diane Levine, a guitarist and pianist, developed gangrene in her right hand, requiring amputation of her right arm at the elbow. Jt. App., at 237-238. Levine filed suit to recover damages for her loss. Her complaint invoked the basic duty of care and duty to warn between drug manufacturer and consumer, not the regulatory duties between drug manufacturer and Food and Drug Administration. She alleged that the drug information failed to instruct the clinician to dilute the drug and to administer the drug through a "running IV"; that the information failed to provide adequate warnings that intra-arterial injection or extravasation could cause irreversible gangrene and loss of limb; and that Phenergan was not reasonably safe due to inadequate warnings and instructions regarding foreseeable risks of harm. Complaint ¶¶ 5-6, Jt. App. 14, 14-15. She alleged that the drug manufacturer had known that its warnings were inadequate and unsafe in this regard since 1987. *Id.*, ¶¶ 10-16, Jt. App., at 15-17. She concluded that Wyeth's "conduct . . . was negligent" and this "negligence and/or gross negligence was the proximate cause of plaintiff's injuries," and she prayed for "appropriate damages for her loss." *Id.*, ¶¶ 19-20, Jt. App., at 17.

Wyeth claims pre-emption because the drug and labeling received pre-market review and approval from the Food and Drug Administration pursuant to the Federal Food, Drug, and Cosmetic Act of 1938, 21 U.S.C. § 355.

Neither the Act in general nor the provisions on pre-market review of new drugs in particular include any term expressly pre-empting state tort remedies. As the Court observed in *Buckman Co. v. Plaintiffs'*

Legal Committee, 531 U.S. 341 (2001), the Act regulates "the relationship between a federal agency and the entity it regulates." 531 U.S., at 347 (discussing parallel provisions on pre-market review of medical devices under the Federal Food, Drug, and Cosmetic Act). It does not purport to regulate the distinct relationship between the manufacturer and the consumer. See also *Desiano v. Warner-Lambert & Co.*, 467 F.3d 85, 94-95 (2d Cir. 2006) (distinguishing claims "premised on traditional duties between a product manufacturer and . . . consumers" and claims premised on a "duty between a manufacturer and a federal agency"), *aff'd by equally divided Court sub nom. Warner-Lambert Co., LLC v. Kent*, 552 U.S. ___, 128 S. Ct. 1168 (2008) (per curiam). Instead, that separate relationship has long been governed by the duty of care and duty to warn under state common law, tort, and products liability. See Section I, *post*, at 6.

The legislative history of the Act, and the concurrent history of cases recognizing and enforcing drug manufacturers' duties to consumers under state law, confirm the fundamental presumption against pre-emption. See Section II, *post*, at 9. This does not surprise. "[T]he regulation of health and safety matters is primarily, and historically, a matter of local concern." E.g., *Hillsborough County v. Automated Medical Laboratories, Inc.*, 471 U.S. 707, 719 (1985); *Rice v. Santa Fe Elevator Corp.*, 331 U.S. 218, 230 (1947). As a significant majority of courts have held, the Federal Food, Drug, and Cosmetic Act sets minimum standards for introduction into interstate commerce, and state laws requiring additional warnings to state consumers do not conflict with the Act. See Section III, *post*, at 19.

ARGUMENT

I. DRUG MANUFACTURERS' PRE-MARKET DUTIES TO THE FOOD AND DRUG ADMINISTRATION ARE SEPARATE AND DISTINCT FROM THEIR POST-MARKET DUTY OF CARE AND DUTY TO WARN THEIR INDIVIDUAL CONSUMERS.

Under the Federal Food, Drug, and Cosmetic Act, drug manufacturers must file an application and receive approval before introducing any new drug into interstate commerce. 21 U.S.C. § 355(a).

The application shall include the drug's composition, how it is manufactured and packaged, the proposed labeling, reports of investigations showing whether the drug is safe for use and effective in use, and samples of the drug if required. *Id.*, § 355(b)(1). Within 180 days, the agency shall either approve the application, or notify the applicant that it may elect a hearing. *Id.*, § 355(c)(1). The agency shall approve the application, unless one of seven enumerated grounds exists. *Id.*, § 355(d). The agency shall not approve the application if the reported investigations were not adequate to show, or there is insufficient information to determine, whether the drug is safe; or the manufacturing and packaging are inadequate; or the agency lacks substantial evidence that the drug will have the effect claimed; or certain patent information is missing; or the proposed labeling is false or misleading in any particular. *Ibid.* The agency may subsequently withdraw approval to engage in interstate commerce under enumerated circumstances. *Id.*, § 355(e). These are disclosures to and duties between regulator and regulated entity, to obtain approval for introduction of the new drug into interstate commerce.

Between drug manufacturer and consumer, however, the drug manufacturer's duties are quite different. The trial court below explained those duties between drug manufacturer and consumer under Vermont law in its instructions to the jury:

> Duty of Care
>
> The manufacturer of a product such as Wyeth has a duty to take reasonable steps to notify users of the product—in this case the medical community—of the risks and dangers of the product and to provide adequate instructions about how to use the product safely. This standard of conduct does not require that useful drugs with dangerous potential be removed from the market. Instead, the law requires that Wyeth exercise reasonable care to warn or protect against the risks.
>
> . . . Warnings for prescription drugs are intended for the physician and his staff whose duty it is to balance the risks against the benefits of various drugs and treatments and to prescribe them and supervise their effects.
>
> Duty to Warn
>
> . . . The manufacturer's duty is to warn of all potential dangers in its prescription drugs that it knew, or in the exercise of reasonable care, should have known to exist. . . .
>
> . . . .
>
> Strict Liability—Failure to Warn
>
> A manufacturer of a product such as Phenergan is responsible for harm to a person caused by a defective product that reaches a user without undergoing substantial change.

Jt. App., at 227, 227-231.

The jury may consider evidence that the drug manufacturer complied with the Food and Drug Administration's requirements, but that evidence does not prove that the drug manufacturer's warnings met its duties to the consumer. *Id.*, at 227-228.

In short, the drug manufacturers' pre-market duties to the Food and Drug Administration in order to secure prior approval for interstate commerce, are separate and distinct from its subsequent, post-market duties to actual consumers under state law. The Federal Food, Drug, and Cosmetic Act does not pre-empt or conflict with these independent duties drug manufacturers have under state law.

II. THE FEDERAL FOOD, DRUG, AND COSMETIC ACT REGULATES DUTIES BETWEEN DRUG MANUFACTURER AND REGULATOR, AND DOES NOT PRE-EMPT DRUG MANUFACTURERS' INDEPENDENT DUTIES TO CONSUMERS UNDER LONG-ESTABLISHED STATE POLICE POWERS.

The Supreme Court of Vermont agreed with the preponderance of courts that the Federal Food, Drug, and Cosmetic Act does not pre-empt state failure-to-warn claims. App. to Pet. for Cert. 15a; see, e.g., *Riegel v. Medtronic, Inc.*, 552 U.S. ___, ___ & n. 11, ___ & n. 16, 128 S. Ct. 999, 1017 & n. 11, 1018-1019 & n. 16 (2008) (Ginsburg, J., dissenting) (collecting cases).

In analyzing whether the Federal Food, Drug, and Cosmetic Act pre-empts a drug manufacturer's duty of care and duty to warn consumers under state laws, Congressional intent is the touchstone. E.g., *Cipollone v. Liggett Group, Inc.*, 505 U.S. 504, 516

(1992); *California Fed. Sav. & Loan Ass'n v. Guerra*, 479 U.S. 272, 280 (1987) (in deciding whether federal law pre-empts state law, "our sole task is to ascertain the intent of Congress"); *Rice*, 331 U.S., at 230 ("the historic police powers of the States [are] not to be superseded by . . . Federal Act unless that [is] the clear and manifest purpose of Congress."); see also *Medtronic, Inc. v. Lohr*, 518 U.S. 470, 485 (1996) (same).

The statute itself is the first indicia of intent. When Congress enacted the Federal Food, Drug, and Cosmetic Act in 1938, it included no provision to pre-empt state law. *Jones v. Rath Packing Co.*, 430 U.S. 519, 538 (1977) ("The FDCA contains no pre-emptive language."); see also *Riegel*, 552 U.S., at ___, 128 S. Ct., at 1016 (Ginsburg, J., dissenting).

Where a statute—such as the Federal Food, Drug, and Cosmetic Act—expresses no intent or purpose to pre-empt state laws, the Court presumes that Congress did not intend to pre-empt states laws. E.g., *Lohr*, 518 U.S., at 485 ("[B]ecause the States are independent sovereigns in our federal system, we have long presumed that Congress does not cavalierly pre-empt state-law causes of action."); *Hillsborough County*, 471 U.S., at 715 ("presumption that state or local regulation of matters related to health and safety is not invalidated under the Supremacy Clause"); *Rice*, 331 U.S., at 230 ("the historic police powers of the States [are] not to be superseded by . . . Federal Act unless that [is] the clear and manifest purpose of Congress."). A long history of state tort remedies–as here–against manufacturers in the area at issue "adds force to the basic presumption against pre-emption." *Bates v. Dow AgroSciences LLC*, 544 U.S. 431, 449 (2005); cf.

Silkwood v. Kerr-McGee Corp., 464 U.S. 238, 251-256 (1984) (Congress assumed that existing state tort remedies would be available). Wyeth faces a "heavy burden of persuasion" to demonstrate the requisite "clear and manifest purpose of Congress" that alone can overcome that presumption. *Johnson v. Fankell*, 520 U.S. 911, 917 (1997); *Rice*, 331 U.S., at 230.

The legislative history of the Act, and the concurrent history of cases recognizing and enforcing drug manufacturers' independent duties to consumers under state law, confirm this fundamental presumption against pre-emption.

A. Federal Food and Drugs Act of 1906

The basic structure of the Food, Drug, and Cosmetic Act and the argument against pre-emption date back over 100 years, to the Federal Food and Drugs Act of 1906, Pub. L. 59-384, ch. 3915, 34 Stat. 768, the predecessor to the Food, Drug, and Cosmetic Act of 1938.

The Federal Food and Drugs Act of 1906 prohibited manufacture of and interstate commerce in adulterated or misbranded foods and drugs, as defined in the act. *Id.*, §§ 1-2, 7-8, 34 Stat. at 768, 769-770 (repealed by Federal Food, Drug, and Cosmetic Act of 1938, Pub. L. No. 75-717, § 902(a), 52 Stat. 1040, 1059). The act did not purport to pre-empt the manufacturer's duty of care and duty to warn its consumers, nor the traditional state laws enforcing those duties. For example, a state law in Wisconsin generally prohibited selling food that contains the preservative benzoate of soda. A federal regulation under the Federal Food and Drugs Act of 1906 provided that addition of the preservative benzoate of soda was not injurious to health and was not

objectionable under the federal act. When a food shipper argued that the federal regulation pre-empted the state law, even as applied to local retail sales, this Court disagreed:

> When objects of commerce get within the sphere of state legislation the State may exercise its independent judgment and prohibit what Congress did not see fit to forbid. . . . The Food and Drugs Act does not interfere with state regulation of selling at retail. [Citations omitted.] Such regulation is not an attempt to supplement the action of Congress in interstate commerce but the exercise of an authority outside of that commerce that always has remained in the states.

Weigle v. Curtice Brothers Co., 248 U.S. 285, 288 (1919); see also *Savage v. Jones*, 225 U.S. 501, 539 (1912) (Federal Food and Drugs Act of 1906 does not pre-empt state statute requiring disclosure of additional matters, *viz.* the product's ingredients, in order to protect against deception and ensure that purchasers are informed about what they are buying by certificate and label requirements).

Accordingly, state-based tort claims proceeded without pre-emption under the predecessor Federal Food and Drugs Act of 1906. See, e.g., *Mazetti v. Armour & Co.*, 75 Wash. 622 (Wash. 1913); *Moehlenbrock v. Parke, Davis & Co.*, 141 Minn. 154 (Minn. 1918); *Kelly v. John R. Daily Co.*, 56 Mont. 63 (Mont. 1919); *Hruska v. Parke, Davis & Co.*, 6 F.2d 536 (8th Cir. 1925); *Portage Markets Co. v. George*, 111 Ohio St. 775 (Ohio 1924); *Machlitt v. Myers*, 23 Ohio App. 160 (Ohio App. 1926); *Coca Cola Bottling Works v. Selvidge*, 4 Tenn. App. 558 (Tenn. Ct. App. 1927); *Ritchie v. Sheffield Farms Co.*, 222 N.Y.S. 724

(N.Y. Mun. Ct. 1927); *Abbott Laboratories v. Lapp*, 78 F.2d 170 (7th Cir. 1935).

B. Federal Food, Drug, and Cosmetic Act of 1938

In 1938, Congress augmented and stiffened the requirements for new drugs by providing for pre-market review to assess safety. Federal Food, Drug, and Cosmetic Act of 1938, Pub. L. No. 75-717, ch. 675, § 505, 52 Stat. 1040, 1052. The act mandated that "[n]o person shall introduce or deliver for introduction into interstate commerce any new drug, unless an application filed pursuant to subsection (b) is effective with respect to such drug." *Ibid.* (codified as amended at 21 U.S.C. § 355(a) ["No person shall introduce or deliver for introduction into interstate commerce any new drug, unless an approval of an application filed pursuant to subsection (b) or (j) is effective with respect to such drug."]).

Congress inserted no pre-emption clause. Drug manufacturers remained subject to tort claims, independent of the new provisions for pre-market review and approval of new drugs. See, e.g., *Wennerholm v. Stanford Univ. Sch. of Med.*, 20 Cal.2d 713 (Cal. 1942); *Wechsler v. Hoffman-La Roche, Inc.*, 99 N.Y.S.2d 588 (N.Y. Sup. 1950); *Fielding v. Superior Ct. (Westwood Pharmaceutical Corp.)*, 111 Cal. App. 2d 490 (Cal. Ct. App. 1952); *E.I. DuPont de Nemours & Co. v. Ladner*, 221 Miss. 378 (Miss. 1954); *Arata v. Tonegato*, 152 Cal. App. 2d 837 (Cal. Ct. App. 1957); *Martin v. Bengue, Inc.*, 25 N.J. 359 (N.J. 1957); *Braun v. Roux Distributing Co., Inc.*, 312 S.W.2d 758 (Mo. 1958).

C. Drug Amendments of 1962

In 1962, Congress further amended the requirements for new drugs by providing that pre-market review assess effectiveness as well. Drug Amendments of 1962, Pub. L. No. 87-781, § 102, 76 Stat. 780, 781. When it did so, Congress expressly stated that "[n]othing in the amendments made by this Act [Drug Amendments of 1962] to the Federal Food, Drug, and Cosmetic Act shall be construed as invalidating any provision of State law which would be valid in the absence of such amendments unless there is a direct and positive conflict between such amendments and such provision of State law." Drug Amendments of 1962, § 202, 76 Stat., at 793; see also *id.*, § 104, 76 Stat. at 784 (amending section 505 of the Federal Food, Drug, and Cosmetic Act on pre-market review of new drugs).

In other words, nothing in the amendments invalidated the numerous provisions of state law enforced by the cases cited above, which clearly had already been valid in the absence of the amendments. There was no direct and positive conflict, and drug manufacturers remained subject to tort claims for failure to meet their duty of care and duty to warn state consumers. See, e.g., *Berry v. American Cyanamid Co.*, 341 F.2d 14 (6th Cir. 1965); *Sterling Drug, Inc. v. Cornish*, 370 F.2d 82 (8th Cir. 1966); *Love v. Wolf*, 249 Cal. App. 2d 822 (Cal. Ct. App. 1967); *Krug v. Sterling Drug, Inc.*, 416 S.W.2d 143 (Mo. 1967); *Toole v. Richardson-Merrell Inc.*, 251 Cal. App. 2d 689 (Cal. Ct. App. 1967); *Fritz v. Parke Davis & Co.*, 277 Minn. 210 (Minn. 1967); *Williams v. Vick Chemical Co.*, 279 F. Supp. 833 (S.D. Iowa 1967); *Bine v. Sterling Drug, Inc.*, 422 S.W.2d 623 (Mo. 1968); *Davis v. Wyeth Laboratories, Inc.*, 399 F.2d 121

(9th Cir. 1968); *Sterling Drug, Inc. v. Yarrow*, 408 F.2d 978 (8th Cir. 1969); *Tinnerholm v. Parke, Davis & Co.*, 411 F.2d 48 (2d Cir. 1969); *Parke-Davis & Co. v. Stromsodt*, 411 F.2d 1390 (8th Cir. 1969); *Grinnell v. Charles Pfizer & Co.*, 274 Cal. App. 2d 424 (Cal. Ct. App. 1969); *Kershaw v. Sterling Drug, Inc.*, 415 F.2d 1009 (5th Cir. 1969); *Schenebeck v. Sterling Drug, Inc.*, 423 F.2d 919 (8th Cir. 1970); *Hornung v. Richardson-Merrill, Inc.*, 317 F. Supp. 183 (D. Mont. 1970); *Croft v. York*, 244 So.2d 161 (Fla. Ct. App. 1971); *Singer v. Sterling Drug, Inc.*, 461 F.2d 288 (7th Cir. 1972); *Stevens v. Parke, Davis & Co.*, 9 Cal. 3d 51 (Cal. 1973); *Redfield v. Mead, Johnson & Co.*, 266 Or. 273 (Or. 1973); *Hoffman v. Sterling Drug, Inc.*, 374 F. Supp. 850 (M.D. Pa. 1974); *Reyes v. Wyeth Laboratories*, 498 F.2d 1264 (5th Cir. 1974); *Crocker v. Winthrop Laboratories, Div. of Sterling Drug, Inc.*, 514 S.W.2d 429 (Tex. 1974); *McEwen v. Ortho Pharmaceutical Corp.*, 270 Or. 375 (Or. 1974); *Whitley v. Cubberly*, 24 N.C. App. 204 (N.C. Ct. App. 1974); *Oresman v. G.D. Searle & Co.*, 388 F. Supp. 1175 (D.R.I. 1975); *Henry v. Richardson-Merrell, Inc.*, 508 F.2d 28 (3d Cir. 1975); *Salmon v. Parke, Davis & Co.*, 520 F.2d 1359 (4th Cir. 1975).

D. Medical Device Amendments of 1976

When Congress enacted the Medical Device Amendments of 1976, it added the only other provision on the effect of the Federal Food, Drug, and Cosmetic Act upon state and local law. Congress limited the scope of that provision to medical devices only:

> SEC. 521. (a) Except as provided in subsection (b), no State or political subdivision of a State may establish or continue in effect with respect

> to a device intended for human use any requirement—
>
> (1) which is different from, or in addition to, any requirement applicable under this Act to the device, and
>
> (2) which relates to the safety or effectiveness of the device or to any other matter included in a requirement applicable to the device under this Act.

Medical Device Amendments of 1976, Pub. L. No. 94-295, § 2, 90 Stat. 539, 574 (adding Section 521 to the Federal Food, Drug, and Cosmetic Act, codified as amended at 21 U.S.C. § 360k(a)).

Congress did not extend this pre-emption to the rest of the Federal Food, Drug, and Cosmetic Act in general and pre-market approval of new drugs in particular. See *Riegel*, 552 U.S., at ___, 128 S. Ct., at 1009 ("if, as the dissent believes, Congress wanted the two regimes to be alike[,] Congress could have applied the pre-emption clause to the entire FDCA. It did not do so, but instead wrote a pre-emption clause that applies only to medical devices."). The cases cited above on drug manufacturers' independent duties to consumers were all on the books when Congress enacted the Medical Device Amendments of 1976. If Congress had wanted to end or restrict drug manufacturers' independent duty of care and duty to warn their consumers, and the history of tort relief for injuries caused by new drugs after the creation of pre-market review in 1938, then Congress would not have written a pre-emption clause limited to medical devices alone.

A recent decision by the Court further illustrates the point in juxtaposition.

Cipollone v. Liggett Group, Inc., 505 U.S. 504 (1992), concerned express pre-emption provisions in two federal laws on cigarette labeling and advertising. The Federal Cigarette Labeling and Advertising Act of 1965 specified the warning to be placed on a package of cigarettes. In a section entitled "Preemption," the act also provided that no other statement shall be required on any cigarette package, and that "[n]o [other] statement related to smoking and health shall be required in the advertising of [those] cigarettes." See Federal Cigarette Labeling and Advertising Act of 1965, Pub. L. 89-92, §§ 4, 5, 79 Stat. 282, 283. The Court held that the first pre-emption provision, of 1965, "only pre-empted state and federal rulemaking bodies from mandating particular cautionary statements and did not pre-empt state-law damages actions." *Cipollone*, 505 U.S., at 519-520.

The act's successor, the Public Health Cigarette Smoking Act of 1969, strengthened the requisite warning's language, and provided instead that "[n]o [other] requirement or prohibition based on smoking and health shall be imposed under State law with respect to the advertising or promotion of [those] cigarettes." See Public Health Cigarette Smoking Act of 1969, Pub. L. 91-222, § 2, 84 Stat. 87, 88 (amending sections 4 and 5). The Court held that the second pre-emption provision, of 1969, did pre-empt claims that state law required post-1969 advertising or promotions to "include[] additional, or more clearly stated, warnings." *Cipollone*, 505 U.S., at 524-525.[3]

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[3] Similarly, *Bates v. Dow AgroSciences LLC*, 544 U.S. 431 (2005) held that a provision of the Federal Insecticide, Fungicide, and Rodenticide Act—that certain States "'shall not impose or continue in effect any requirements for labeling or

Here, in contrast, Congress has inserted no such pre-emption provision, of either kind, regarding labeling approved under the Federal Food, Drug, and Cosmetic Act. Congress did not prohibit any other "requirement or prohibition . . . imposed under state law," as in the 1969 act. Congress did not prohibit any other statements in advertising, as in the 1965 act--which would not have pre-empted state damages actions in any case. Diane Levine proved that additional or more clearly stated warnings were required, and the Federal Food, Drug, and Cosmetic Act nowhere pre-empts the drug manufacturer's basic duties to its consumers under state law.

III. THE FEDERAL FOOD, DRUG, AND COSMETIC ACT SETS MINIMUM STANDARDS FOR INTRODUCTION OF NEW DRUGS INTO INTERSTATE COMMERCE, AND STATE LAWS REQUIRING ADDITIONAL WARNINGS TO STATE CONSUMERS DO NOT CONFLICT WITH THE ACT.

Courts have frequently recognized that federal safety regulations between regulator and regulated entity set minimum standards, and that common-law tort claims could require stricter standards so long as they did not conflict with the federal regulatory scheme. E.g., *Geier v. American Honda Motor Co., Inc.*, 529 U.S. 861, 867-868 (2000) (recognizing that federal safety regulations set minimum standards and that common-law tort claims could require

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packaging in addition to or different from those required under this subchapter'"—pre-empted common-law actions. 544 U.S., at 443 (discussing 7 U.S.C. § 136v(b)).

stricter standards so long as they did not conflict with the federal regulatory scheme).

Accordingly, most courts have held that the Federal Food, Drug, and Cosmetic Act's regulation of prescription drugs establishes minimum standards, for the introduction of new drugs into interstate commerce, and that a drug manufacturer's compliance with those minimum duties to the Food and Drug Administration does not pre-empt or repeal the drug manufacturer's separate duty of care and duty to warn its consumers, nor absolve the manufacturer of tort liability for failure to meet those independent duties. See, e.g., *Brochu v. Ortho Pharmaceutical Corp.*, 642 F.2d 652, 658 (1st Cir. 1981) (rejecting argument that warnings were adequate if drafted by the Food and Drug Administration as required uniform labeling); *Salmon v. Parke, Davis & Co.*, 520 F.2d 1359, 1362 (4th Cir. 1975) ("In North Carolina, as elsewhere, compliance with federal laws and regulations concerning a drug, though pertinent, does not in itself absolve a manufacturer of liability."); *Hurley v. Lederle Laboratories*, 863 F.2d 1173, 1177 (5th Cir. 1988) ("FDA regulation does not generally preempt stricter state law standards for medical products."); *Hill v. Searle Laboratories*, 884 F.2d 1064, 1068 (8th Cir. 1989) ("FDA approval is not a shield to liability. [Citations omitted.] FDA regulations are generally minimum standards of conduct unless Congress intended to preempt common law, which Congress has not done in this area."); *Wells v. Ortho Pharmaceutical Corp.*, 788 F.2d 741, 746 (11th Cir.) ("An FDA determination that a warning is not necessary may be sufficient for federal regulatory purposes but still not be sufficient for state tort law purposes."), cert. denied, 479 U.S. 950 (1986); *Motus v. Pfizer Inc.*, 127 F. Supp. 2d 1085, 1096 (C.D. Cal.

2000) ("Several other courts have determined that FDA requirements are minimal standards and that FDA approval is not a shield to liability."); *Caraker v. Sandoz Pharmaceuticals Corp.*, 172 F. Supp. 2d 1018, 1033 (S.D. Ill. 2001) ("The reason why many courts find no preemption is that the FDA's drug labeling decisions impose only 'minimum' standards that are open to supplementation by state law through a jury's verdict enforcing a manufacturer's common law duty to warn."); *Kociemba v. G.D. Searle & Co.*, 680 F. Supp. 1293, 1299 (D. Minn. 1988) ("widely held view that FDA regulation of prescription drugs establishes minimum standards, both as to design and warning"); *Spychala v. G.D. Searle & Co.*, 705 F. Supp. 1024, 1030 (D.N.J. 1988) ("There is less sense of a comprehensive regulatory scheme, however, than there is of labeling requirements which must be met at a minimum and certainly no suggestion that if additional requirements were imposed by the states any FDA regulatory scheme for IUD design and labeling would be destroyed. Courts have held with some consistency that while FDA regulation of prescription drugs may establish minimum standards for product design and warning labels, compliance does not necessarily absolve a manufacturer of tort liability"); *Feldman v. Lederle Laboratories*, 125 N.J. 117, 141 (N.J. 1991) (compliance with FDA regulations may establish that the manufacturer met the appropriate minimum standards of due care, but compliance does not necessarily absolve the manufacturer of all liability), cert. denied, 505 U.S. 1219 (1992). But cf. *Colacicco v. Apotex, Inc.*, 521 F.3d 253, 271-272 & n. 17 (3d Cir. 2008) (where the FDA has publicly rejected the need for a warning that plaintiffs argue state law requires, holding that, "under the circumstances of this case, the plaintiffs'

failure-to-warn claims are preempted by the FDA's actions taken in accordance with its statutory authority," and expressly not deciding "whether the FDA's mere approval of drug labeling is sufficient to preempt state-law claims alleging that the labeling failed to warn of a given danger, [or] whether FDA approval of drug labeling constitutes minimum standards in the absence of the FDA's express rejection of a specific warning," and distinguishing the Supreme Court of Vermont's decision in *Wyeth* on these grounds).

Recognizing the drug manufacturer's independent duties to consumers to provide adequate warning at all times after approval, the Food and Drug Administration's own regulations provide for immediate label changes without prior approval to provide adequate warnings:

> (A) To add or strengthen a contraindication, warning, precaution, or adverse reaction;
>
> (B) To add or strengthen a statement about drug abuse, dependence, psychological effect, or overdosage;
>
> (C) To add or strengthen an instruction about dosage and administration that is intended to increase the safe use of the drug product;
>
> (D) To delete false, misleading, or unsupported indications for use or claims for effectiveness; or
>
> (E) Any labeling change normally requiring a supplement submission and approval prior to distribution of the drug product that FDA specifically requests be submitted under this provision.

21 C.F.R. § 314.70(c)(6)(iii)(A)-(E); accord *id.*, § 314.70(b)(2)(v)(A) (exempting labeling changes

under § 314.70(c)(6)(iii) from the requirement of a supplemental application and approval prior to making the labeling change); *id.*, § 314.70(c)(4) (exempting labeling changes under § 314.70(c)(6) from the requirement to wait 30 days before making the change).

The regulation confirms that neither the Federal Food, Drug, and Cosmetic Act nor the implementing regulations preclude additional labeling in compliance with the drug manufacturer's duty of care and duty to warn. Again, the federal standards established between drug manufacturer and regulator are minimal standards for introducing the new drug into interstate commerce; they do not pre-empt the drug manufacturer's separate duties to consumers under state laws. With respect to labeling in particular, there is no conflict between drug manufactures' duties to consumers under state law and drug manufacturers' separate regulatory duties under the Federal Food, Drug, and Cosmetic Act.

The cases are legion where new drugs that the Food and Drug Administration has approved for introduction into interstate commerce—duties between drug manufacturers and the Food and Drug Administration having been met–subsequently cause great harm or death to individual consumers because the pharmaceutical company failed its separate duty of care and duty to warn the individual consumer. These cases demonstrate the importance of drug manufacturers' continuing and independent duties to consumers under state law.

One illustrative example concerns the drug DES. In the late 1940s, the Food and Drug Administration approved drug manufacturers' applications to sell diethylstilbestrol (DES) in interstate commerce. See,

e.g., *Collins v. Eli Lilly Co.*, 116 Wis. 2d 166, 179 (Wis. 1984). Pharmaceutical companies marketed DES for use by pregnant women to prevent miscarriage. *Ibid.* In 1952, the Food and Drug Administration decided that DES was no longer a "new drug," and drug manufacturers could sell it in interstate commerce without prior testing and new drug applications under 21 U.S.C. § 355(b). See *id.*, at 179; *Sindell v. Abott Laboratories*, 26 Cal. 3d 588, 593 (Cal. 1980). DES, however, caused growths and cancer in daughters of mothers who took DES during pregnancy, which did not manifest until after a minimum period of latency of 10 or 12 years. See, e.g., *Sindell*, 26 Cal. 3d, at 594. Medical studies questioned the therapeutic value of the promoted use to prevent miscarriage. E.g., *Collins*, 116 Wis. 2d, at 179, n. 6 (citing medical study published in 1953). In 1971, the Food and Drug Administration ordered drug manufacturers to cease selling DES for this use, and to warn physicians and the public that pregnant women should not use it. *Id.*, at 179.[4] Cases such as this illustrate the critical importance of a drug manufacturer's continuing and independent duties to consumers under state law, when post-market experience subsequently proves that the new drug should not be used as promoted and advertised.

CONCLUSION

Every day in this country, the ordinary consumer has no choice but to trust strangers to provide them

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[4] The DES cases also revealed that drug manufacturers actually purchase insurance in anticipation of state tort actions. See, e.g., *Schering Corp. v. Home Ins. Co.*, 712 F.2d 4, 7-8 (2d Cir. 1983); *Eli Lilly & Co. v. Home Ins. Co.*, 653 F. Supp. 1, 3-5 (D.D.C. 1984).

with uncontaminated food, good medicine, honest financial services, safe cars, and the whole host of other products and services associated with modern life. Every day, manufacturers' fundamental duty of care and duty to warn this ordinary consumer are critical consumer remedies and protections. With the Federal Food, Drug, and Cosmetic Act, Congress enacted minimum standards of safety and efficacy for sales of new drugs in interstate commerce, but it nowhere pre-empted the drug manufacturers' separate duty of care and duty to warn the individual consumer. Under the Federal Food, Drug, and Cosmetic Act, federal pre-market regulatory review and approval, and state common-law remedies and duties in the marketplace, exist in concert to secure a fair, just, and safe marketplace for all consumers.

For the reasons set forth above and in the Brief for Respondent, the judgment of the Supreme Court of Vermont should be affirmed.

Respectfully submitted,

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In The Supreme Court of the United States

WYETH,

Petitioner,

v.

DIANA LEVINE,

Respondent.

ON WRIT OF CERTIORARI
TO THE UNITED STATES COURT OF APPEALS
FOR THE SUPREME COURT OF VERMONT

BRIEF OF DES ACTION AS *AMICUS CURIAE* IN SUPPORT OF RESPONDENT

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INTEREST OF THE AMICUS CURIAE[1]

DES Action is a national, non-profit organization of over two thousand members from all fifty states. Its purpose is to provide education and support for the two and one-half million daughters and sons exposed *in utero* to diethylstilbestrol ("DES"), a synthetic estrogen approved by the Food and Drug Administration ("FDA") and prescribed to pregnant women between 1948 and 1971 for the prevention of miscarriage. DES was approved by the FDA and promoted by dozens of manufacturers for over two decades as a miscarriage preventative without a single controlled study demonstrating its efficacy or safety in animals or humans. Today, the FDA, the National Institutes of Health, the Centers for Disease Control, and the World Health Organization unanimously agree that the use of DES in pregnancy is of no value in preventing miscarriage and that DES is a transplacental carcinogen and teratogen.

For over thirty years, DES Action has represented the DES-exposed, both in the United States and internationally, by creating, maintaining, and providing a repository of health information, a list of DES-knowledgeable healthcare providers across the country, counseling and support groups, and advocating for research into the effects of DES.

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[1] The parties have consented to the filing of this *amicus* brief. Pursuant to Rule 37.6, this *amicus* states that this brief was not authored in whole or in part by counsel for any party, and that no person or entity other than this *amicus* and its counsel made a monetary contribution to the preparation or submission of this brief.

DES Action communicates with its members and with the DES-exposed through its website and associated chat groups, through its newsletter, and by events open to members and the public. Thousands each year contact DES Action for information and guidance regarding their DES injuries by phone, letter, or through DES Action's website, www.desaction.org.

DES Action files this *amicus* brief to protect the legal rights of the hundreds of DES daughters, sons, and grandchildren yet to realize or manifest their DES injuries and yet to seek compensation for their injuries and malformations from their exposure *in utero* to DES. The teratogenic effects of *in utero* DES exposure often take decades to manifest. Each year since 1971, when the connection between *in utero* DES exposure and vaginal cancer was made and the FDA, under pressure from Congress, declared it contraindicated for pregnant women, the medical literature reports new adverse manifestations of DES exposure and DES injuries. Recently it has been found that DES daughters have an increased risk of breast cancer. See, e.g., Julie R. Palmer, et al., "Prenatal Diethylstilbestrol Exposure and Risk of Breast Cancer," 15 Cancer, Epidemiology, Biomarkers & Prevention 1509 (2006). Many DES daughters, having waited until their thirties or forties to have children, are only now discovering obstacles to fertility from their DES-malformed reproductive tracts; others will develop cervical and vaginal DES-related cancer in the future. Should unconditional or blanket pre-emption be declared by this Court, DES victims shall be without compensation for their infertility, cancer,

preterm births, ectopic pregnancies, and other DES-caused injuries.

SUMMARY OF ARGUMENT

This *amicus* asks the Court to deny the position of Petitioner and its *amici* and affirm the Supreme Court of Vermont, rejecting blanket pre-emption in pharmaceutical cases. The briefs of Petitioner and its *amici*, most notably the brief of the United States, advocate that the FDA's balancing of risks and benefits weighs in favor of blanket pre-emption without conditions. All now agree that the FDA should never have approved DES for use in pregnancy, and that it should have been taken off the market decades before the hue and cry from Congress forced the FDA to act. See Hearing Before the Subcommittee on Government Operations 92nd Congress Nov 11, 1971.

This amicus opposes the concept that FDA approval of a drug unconditionally pre-empts state law tort claims. DES is, this *amicus* believes, the most telling example of a bureaucratic error by the FDA in its history. The FDA's mission of scrutiny and supervision of drug manufacturers and their economic incentives to over-promote drugs was completely suspended. The DES experience reveals that pre-emption would make no distinction between passive and active FDA enforcement; no difference between a manufacturer following federal regulations and a manufacturer flouting them; no difference between a drug still in its experimental phases and a drug "generally recognized as safe" for decades; no difference between a drug that is

subjected to the rigorous examination and give and take of its therapeutic index and one that is summarily and cursorily rubber-stamped; no difference between the drug in the current FDA approval process and a drug approved by the FDA sixty years ago. Blanket pre-emption would cast too wide a net.

FDA pre-emption is not appropriate when, as with DES, animal and human studies regarding safety were omitted from consideration, clinical trials were never required by the FDA, and the only controlled, double-blind study conducted revealed DES to be ineffective for eighteen years before its recall. When the FDA's review of a drug is inadequate, either through manufacturer under-reporting, lack of resources, or inadvertence, as all were with DES, there must be a point where the tort system should evaluate a drug company's conduct in exercising due care and prudence to ensure that the safety of their product was unreasonable in accordance with the state of the art at the time. FDA law concerns scientific proof of the efficacy and safety of a drug. Tort law concerns the conduct of the manufacturer. Different interests and perspectives. The FDA's mission is the health of the nation; drug manufacturers are interested in profit for their shareholders.

ARGUMENT

I. THE DES STORY

"For over three decades, doctors prescribed diethylstilbestrol to nearly five million women in the

United States as a way to prevent pregnancy problems such as miscarriage . . . . But the synthetic estrogen also known as DES didn't work." Reeves v. Eli Lilly & Co., 368 F. Supp. 2d 11, 12 (D.D.C. 2005).

DES was synthesized in the 1930's by Sir Charles Dodds, who was seeking a cheap estrogen which could be taken orally; even Dr. Dodds himself did not believe in giving synthetic estrogen to otherwise healthy women. See Barbara Seaman, The Greatest Experiment Ever Performed on Women 36-37 (2003); Roberta Apfel, M.D. and Susan Fisher, M.D., DES and the Dilemmas of Modern Medicine 13 (1984). Because British law did not allow patents on discoveries financed by government grants, the drug was never patented, and as such was sold under a multitude of labels. See id. Estrogens were long known as potential teratogens and carcinogens. See Seaman at 44. By 1939, professors Greene, Burrill, and Ivy of Northwestern University found that the offspring of rodents given DES while pregnant showed significant deformities of their reproductive organs. See R.R. Greene, et al., "Experimental Intersexuality: The Paradoxical Effects of Estrogen on the Sexual Development of the Rat," 74 Anatomical Record 4 (May 1939). Furthermore, DES resists attempts by the body to metabolize or excrete it, and so regular ingestion of DES caused a significant amount of the drug to accumulate in the body. See K.K. Chen, M.D., "The New Synthetic Estrogen, Stilbestrol," Quarterly Bulletin Ind. Univ. Med. Ctr. 15, 16 (April 1941).

In the late forties, favorable reports on DES as an anti-abortifacient were presented and packaged

to the FDA, coordinated by a committee of drug company officials, under the auspices of what would become the American Pharmaceutical Society; this committee pooled favorable research and excluded unfavorable criticism. Not a single drug company performed any independent research, much less a controlled study or clinical trial, to determine the safety and efficacy of DES See Stephen Fenichell and Lawrence S. Charfoos, Daughters at Risk: A Personal D.E.S. History 34-36 (1981).

When DES was first approved, the FDA was evaluating a crush of applications with its new responsibility to test drugs for safety. See FDA, "New Drug Application Approvals and Receipts, Including New Molecular Entities, 1938 to Present," available at http://www.fda.gov/oc/history /NDAapprovals.html (last visited July 23, 2008). Testing for efficacy was not required until 1962. See Thaddeus H. Grasela, Jr., "A Nationwide Drug Surveillance Network," Pharmacoepidemiology 171 (Stanley A. Edlavitch, ed. 1987).

In those days, the FDA had a tiny fraction of its present manpower and resources and could not give DES anywhere near the level of scrutiny that drugs receive today, much less the investigation that it deserved. The FDA did not even require proof of efficacy until 1962, and at that point grandfathered DES for all uses.

In 1947, as the manufacturers of DES were gearing up for FDA approval of DES for use in pregnancy, Dr. Rosenblum, a leading obstetrician and gynecologist of Cedars of Lebanon Hospital in

Los Angeles wrote an editorial requesting that specific investigation be done to determine if DES would cause cancer or hormonal imbalances in the exposed offspring, asking the specific questions:

1. Will diethylstilbestrol in large dosages cause pituitary or other glandular imbalance which will become manifest later in life?

2. Is diethylstilbestrol in such large dosages carcinogenic, and as such unsafe to give even to pregnant women?

See Gordon Rosenblum and Eugene Melinkoff, "Preservation of Threatened Pregnancy With Particular Reference to the Use of Diethylstilbestrol," 55 Western J. of Surgery, Obstetrics, & Gynecology 597 (1947). Neither the drug companies nor the FDA considered these questions, nor did the FDA look outside the submissions to the dozens of reports in the literature critical of DES's efficacy and safety at the time. See Appendix 1. The DES manufacturers relied on cherry-picked studies showing the safety of the new indication. See Fenichell and Charfoos at 51. DES was approved for use in pregnancy on May 25, 1947.

The pregnancy dosage recommendations began at five milligrams, and increased to over one hundred milligrams per day. For purposes of illustration, comparing the current dosage of estrogen in a birth control pill with DES, a pregnant woman on DES was ingesting the estrogenic

equivalent of hundreds of birth control pills daily. See Pat Cody, DES Voices: From Anger to Action 75 (2008). A child *in utero* would essentially bathe in estrogen. At those doses, its developing estrogen-sensitive reproductive organs in their embryonic formation would be over-stimulated and malformed by the excess of hormones. See id.

The FDA, without any consultation with the obstetrical and gynecological community, without any experts in obstetrics and gynecology within the agency, and without the currently employed advisory panels with specialized knowledge of past research in the field, rubber-stamped DES for use in pregnancy. Following DES's introduction as a miscarriage preventative came a cavalcade of critical studies showing the dangers of using DES in pregnancy, which the FDA similarly ignored:

- In 1949, estrogens were found to pass through the placenta in guinea pigs, causing reproductive anomalies in the offspring. See H. Burrows, "Oestrogens," Biological Action of the Sex Hormones (1949).

- In 1950, research into minks fed DES found that DES inhibited their reproduction and caused uterine anomalies in the offspring. See Robert K. Enders, "Mink Production in Relation to Stilbestrol" 16 Fur Journal 7 (1950).

- In 1953, researchers at the University of Chicago undertook the first and only double-blind, controlled study of the efficacy of DES

for prevention of miscarriage. The study found that the women given a placebo had more live births than the women given DES; this study found that DES was ineffective to prevent miscarriages. See W.J. Dieckmann, M.D., et al., "Does the Administration of Diethylstilbestrol During Pregnancy Have Therapeutic Value?" 66 Am. J. Obstetrics & Gynecology 1062 (1953). Other reported studies also concluded that DES was of no value in preventing miscarriage. See, e.g., James Ferguson, "Effect of Stilbestrol on Pregnancy Compared to the Effect of A Placebo," 65 Am. J. Obstetrics & Gynecology 592 (1953).

- In 1959, the United States Department of Agriculture, found DES to be a carcinogen when used in animal feed for chicken and sheep, and banned the use of DES in feed for those animals. See Apfel and Fisher at 14.

- Also in 1959, doctors in Philadelphia reported actual reproductive malformations in DES daughters. See Alfred M. Bongiovanni, et al., "Masculinization of the Female Infant Associated with Estrogenic Therapy Alone During Gestation: Four Cases," 19 J. Clinical Endocrinology and Metabolics 1004 (1959).

- By 1959, enough women had been exposed to DES *in utero* that doctors could have noticed abnormalities in those women's reproductive organs through a simple colposcopic examination; abnormalities appear in up to

sixty percent of all women exposed to DES. See Arthur Herbst, "Vaginal and Cervical Abnormalities After Exposure to Diethylstilbestrol In Utero," 40 Obstetrics & Gynecology 287 (1972). Since the FDA had declared the drug safe in 1952, no one revisited the issue, and pregnant women and their daughters continued to be exposed to DES for an additional twelve years in the face of mounting adverse reports.

- In the early 1960's, the world awoke to the risk of teratogenesis from the use of Thalidomide in pregnancy, alerting the medical community to the danger of prescribing medications during pregnancy. At that time, the scientific community recommended that all drugs given to pregnant women be re-evaluated to determine if they had trans-placental side effects. See, e.g., Frank Moya, M.D. and Virginia Thorndike, M.D., "Passage of Drugs Across the Placenta," 84 Am. J. Obstetrics & Gynecology 1778 (1962). Both the FDA and the manufacturers ignored this warning.

Timelines with the relative studies regarding safety, efficacy, and transplacental capabilities of DES ignored by the FDA are attached as Appendix 1.

Naturally, without the FDA's oversight, the producers of DES made no effort to alert the government or the medical community of the drug's dangers:

> During the period defendants marketed DES, they knew or should have known that it was a carcinogenic substance, that there was a grave danger after varying periods of latency it would cause cancerous and precancerous growths in the daughters of the mothers who took it, and that it was ineffective to prevent miscarriage. Nevertheless, defendants continued to advertise and market the drug as a miscarriage preventative. They failed to test DES for efficacy and safety; the tests performed by others, upon which they relied, indicated that it was not safe or effective. In violation of the authorization of the Food and Drug Administration, defendants marketed DES on an unlimited basis rather than as an experimental drug, and they failed to warn of its potential danger.

Sindell v. Abbott Laboratories, 607 P.2d 924, 926 (Cal. 1980). In fact, drug company promotional literature continued to state that DES was the most effective drug to prevent miscarriage. See, e.g., Eli Lilly and Company, De Re Medica 211 (1953). DES manufacturers recommended the prophylactic use of DES, and even recommended DES to women who had no indications of threatened miscarriage. The only warnings and contraindications for DES required by the FDA prior to 1968 regarded headache and nausea, and after that there was only an indeterminate warning as to some unnamed risk to a fetus without specifying likelihood or severity.

Physicians' Desk Reference 819-20 (23d ed. 1969) A 1967 study by the National Academy of Sciences classified DES as ineffective, below even the class of "probably effective." See Cynthia Orenberg, DES: The Complete Story 123 (1981).

In 1971, two doctors from Massachusetts General Hospital – not the drug companies, not the FDA – broke the news in the New England Journal of Medicine that DES was a carcinogen to the exposed daughters. See Arthur Herbst, et al., "Adenocarcinoma of the Vagina," 284 New Eng. J. Med. 878 (1971). The DES tragedy became front-page news. Only after Congress held hearings on DES did the FDA take action and issue a contraindication for use in pregnancy, resulting in DES's removal from the market. Even then, the FDA, after notification the cancer reports, did nothing for six months. See Fenichell and Charfoos at 92-96, 120. By that time, the Centers for Disease Control estimate that between five and ten million women were exposed to DES. See CDC, "About DES," available at http://www.cdc.gov/des/ consumers/about/index.html (last visited July 21, 2008).

DES has now been specifically recognized by Congress as a public health problem. See, e.g., 105 P.L. 340 (1998) (approving funds for DES research). The Centers for Disease Control has DES education as part of its mission. See CDC, "About DES," http://www.cdc.gov/des/ consumers/about/index.html (last visited August 4, 2008). The National Institutes of Health's National Cancer Institute is similarly tasked with dealing with the fallout of the

DES tragedy. See NIH, "DES: Questions and Answers," http://www.cancer.gov/cancertopics/factsheet/Risk/DES (last visited August 4, 2008).

II. PRE-EMPTION SHOULD NOT BE APPLIED TO CURRENT CLAIMS BASED ON FDA APPROVAL OVER SIXTY YEARS AGO

An agency's decision leads to pre-emption "where it is 'impossible for a private party to comply with both state and federal requirements' . . . or where state law 'stands as an obstacle to the accomplishment and execution of the full purposes and objectives of Congress.'" Sprietsma v. Mercury Marine, 537 U.S. 51, 64 (U.S. 2002) (citations omitted). DES victims were exposed thirty to fifty years ago, when the drug manufacturers could have: 1) strengthened their warnings without seeking prior FDA approval for those changes; 2) the DES manufacturers could have adequately tested the drug and found its dangers without prior FDA approval; 3) the DES manufacturers could have changed their literature to include reports of teratogenesis and carcinogenesis without prior FDA approval; 4) DES manufacturers could have stated in their literature that DES that there had been no adequate controlled testing for safety and efficacy without prior FDA approval; 5) the DES manufacturers could have withdrawn the drug without prior FDA approval or anyone suffering from removal from the market as DES was ineffective. As such, it makes little sense for there to be implied pre-emption based on considerations the FDA did not have at the time of approval.

Before 1962, drugs were not required to be tested for efficacy. As such, Congress's intent for the FDA did not conflict with state law tort principles requiring drug companies to make effective drugs or test for long-term safety; the FDA simply was not making these requirements or involved in policing them. Courts have found that, until the FDA makes a determination regarding a drug, the manufacturer's obligations to make it safe and effective under state standards still apply. See Tucker v. SmithKline Beecham Corp., 2008 U.S. Dist. LEXIS 55919 at *29-31 (S.D. Ind. July 18, 2008). With DES, there was no new determination that could have possibly made the FDA's position conflict with state law liability; the only time the FDA acted was to contraindicate DES.

The FDA is a reactive, not proactive, agency when it comes to drug safety; the FDA does not ferret out adverse effects for itself, but waits for drug companies to provide that information. When the makers of DES buried the studies adverse to DES and failed to provide the FDA with further information, those manufacturers made the further investigation of DES less likely. Government bureaucracies make mistakes; mistakes are inherent in the system. When such mistakes happen, thousands suffer. Giving the FDA's ignorance of the dangers of DES, pre-emptive power would reward the drug houses for their negligence in the face of administrative failure.

III. THERE IS NO RECOURSE FOR DES DAUGHTERS WITHOUT RESORT TO SUIT; THE FDA'S ENFORCEMENT POWERS CANNOT APPROACH ADEQUATE COMPENSATION

At least one industry advocate before this Court sharing Petitioner's views claimed that there "are remedial mechanisms still available to the FDA" and that the FDA has "pretty broad remedial authority and that it extends to some form of restitution to the victims," and as such, pre-emption of tort suits does not leave victims of drugs such as DES daughters without remedy. See Transcript of Oral Arguments, pg. 55, Warner-Lambert v. Kent, No. 06-1498 (S. Ct. 2008) (Carter G. Phillips, Esq., for the petitioner in that case). Obviously, this deception was meant to convince the Court of an adequate alternative to the tort system. Any claim that the FDA can provide restitution to victims is ludicrous and misleading. Mr. Phillips knows better. When a DES daughter finds out that she is infertile or requires reproductive assistance, she is often on her own to seek compensation for treatment. Even presuming that the FDA might, despite haying failed to do so for three decades, pursue the manufacturers of DES for their crimes in misbranding and over-promoting the drug, the sanctions allowed to the FDA are, when available, paltry, and completely insufficient to compensate the injured party.

If a drug company violates 21 U.S.C. § 331 and 332, the FDA may seek restitution for the victims of the mislabeling, but such repayments are not guaranteed. See United States v. Purdue

Frederick Co., 495 F. Supp. 2d 569, 574 (W.D. Va. 2007) (denial of restitution to insurers for misbranding of Oxycontin); see also United States v. Lane Labs-USA, Inc., 427 F.3d 219, 223 (3d Cir. 2005) (Government *may* ask a court for restitution). Restitution under civil principles of equity is limited to reimbursement of the purchase price and potential disgorgement of profits. See Lane Labs, 427 F.3d at 222. Neither a refund of the purchase price nor disgorgement of profits would ever come close to compensating a single victim for cancer, hysterectomy, or infertility.

Conceivably, the FDA could also seek restitution through 18 U.S.C. § 3663,[2] but this method first requires the government to charge the manufacturers of DES with a felony, a step unlikely to occur for pragmatic reasons, and obtain a conviction, where the burden of proof is far greater than in a civil suit. Even if such a conviction were obtained, the damages would be limited. The Eleventh Circuit holds that criminal restitution must be limited to medical bills only. See United States v. Husky, 924 F.2d 223, 227 (11th Cir. 1991). This leaves the infertile DES daughter without compensation for *in vitro* fertilization, assisted reproductive therapy, adoption expenses, surrogacy expenses, and all claims of pain and suffering. In interpreting 18 U.S.C. § 3663 with regard to the

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[2] In fact, the First Circuit denies equitable restitution for medical device cases and only provides restitution with a felony conviction. See Talbott v. C.R. Bard, Inc., 63 F.3d 25, 31 (1st Cir. 1995). It is likely that, at least in the First Circuit, civil restitution is unavailable to the FDA for victims of defective drugs.

related field of medical devices, the Third Circuit held that "[t]he act does not permit the FDA to require companies to compensate victims for their medical expenses or for the pain and suffering resulting from a device failure." Michael v. Shiley, Inc., 46 F.3d 1316, 1321 (3d Cir. 1995).

IV. DES DAUGHTERS HAVE RELIED ON TORT COMPENSATION FOR OVER THIRTY YEARS; ANY PRE-EMPTIVE POWER OF THE FDA'S CONSIDERATION SHOULD NOT BE GIVEN RETROACTIVE EFFECT

For the last thirty years, thousands of injured DES daughters have received tort compensation from the manufacturers of DES and their insurers for their costs, including reproductive assistance such as *in vitro* fertilization, adoption, or surrogacy. Those DES daughters who suffer from cancer have also received compensation for their medical bills.[3] To deny the remaining daughters and sons whose claims have not yet materialized from similar compensation based on the findings of the FDA over fifty-five years ago insulates drug manufacturers from obligations all have acknowledged they have had for decades.

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[3] The medical costs of cancer can be ruinous even to a family with insurance; in 2001, half of all bankruptcy filings were in part due to medical bills, even though 75% of those bankrupt had medical insurance. See David U. Himmelstein, et al., "Illness And Injury As Contributors To Bankruptcy," MarketWatch, available at http://content.healthaffairs.org/cgi/reprint/hlthaff.w5.63v1.pdf (Feb. 2, 2005).

This Court, in Chevron Oil Co. v. Huson, 404 U.S. 97 (U.S. 1971), established three principles for when precedents should be applied retroactively: 1) the decision must establish a new rule of law, 2) whether retrospective application will forward or impede the efforts of justice, taking into account the prior history of the rule, and 3) whether inequity will result from retroactive application of the rule. See 404 U.S. at 106-7. In this case, all of these aspects are in favor of prospective application (should pre-emption be applied, which this *amicus* opposes) and allowing DES daughters to continue their efforts for compensation.

Any ruling in favor of pre-emption would express a new principle of law. This Court has been explicit that it has not yet ruled on the FDA's pre-emption of pharmaceutical products cases. See Reigel v. Medtronic, Inc., 128 S. Ct. 999, 1009 (2008) ("It has not been established . . . that no tort lawsuits are pre-empted by drug or additive approval under the FDCA.").

Second, retroactive application will not promote the efforts of justice. DES's placement on the market for use in pregnancy and its maintenance on the market was the product not just of the FDA's oversight, but of continued negligence and willful blindness by the companies who made it. DES manufacturers systematically ignored and suppressed contrary information, see Appendix 1, to continue selling their product in a dangerous manner. Justice is not promoted by papering over their negligence.

Third, "prospective safeguards do not affect the inequities of retroactive application." American Trucking Ass'n v. Smith, 496 U.S. 167, 183 (U.S. 1990). The creation of a class of DES haves and have nots should militate against retroactive application of any pre-emption doctrine. This is true not just for DES but for the scores of other demonstrably defective drugs where many have rightfully recovered for their injuries but others similarly situated will not.

CONCLUSION

When a person is mugged in front of a sleeping policeman, the policeman's virtual presence but inaction does not vitiate the culpability of the mugger nor does it ratify the robbery. The FDA's culpability for DES was being asleep at the switch while drug companies sold a known teratogen to pregnant women. The goals of tort law, are different from the goals of the FDA, and without express pre-emption by Congress, it cannot be assumed that the FDA is the sole recourse for the DES-exposed, especially since the FDA is unable to compensate their injuries.

For the reasons stated above, DES Action requests that this Court affirm the decision of the Supreme Court of Vermont.

RESPECTFULLY
SUBMITTED,

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APPENDIX 1

TABLE A

Publications Regarding the Carcinogenic Properties of Estrogens Such as DES

1932:
A. Lacassagne, "Apparition de Cancers de la Mamelle Chez la Souris, Male, Soumise & DES Injections de Foliculine," 195 Compte Rendu Hebdomadaires de Séance et Memoires de la Societe de Biologie 630 (1932)
Summary: Estrogens induced mammary cancer in mice.

1933:
Milton Overholser and Edgar Allen, "Ovarian Hormone and Traumatic Simulation of Monkey's Cervix to a Condition Resembling Early Cancer," 30 Proceedings of the Soc. for Experimental Biology and Med. 353 (1932)
Summary: Ovarian hormones stimulate a monkey's cervix in a way similar to cancer.

1936:
Gardner, et al., "Cancer of the Mammary Glands Induced in Male Mice Receiving Estrogenic Hormone," 21 Archives of Pathology 265 (1936)
Summary: Estrogen causes cancer of the mammary glands in female mice.

TABLE A

Publications Regarding the Carcinogenic Properties of Estrogens Such as DES

1936:
Frederick Hisaw and Frederick Ledrugm, "Squamous Metaplasia in the Cervical Glands of Endocrinology in the Monkey Following Oestrin Administration," 20 Endocrinology 228 (1936)
Summary: Estrogen induces squamous metaplasia in a monkey's cervix.

1939:
C.L. Buxton and Earl Engle, "Effects of the Therapeutic Use of Diethylstilbestrol," 113 J. Am. Med. Ass'n 2318 (1939)
Summary: Expressed concerns of diethylstilbestrol's toxic effect.

Charles Geschickter, "Mammary Carcinoma in the Rat with Metastasis in the Rat with Metastasis Induced by Estrogen," 89 Science 35 (1939)
Summary: Estrogen induces mammary cancer in rats.

1940:
Michael B. Shimkin and Hugh G. Grady, "Carcinogenic Potency of Stilbestrol and Estrone in Strain C(3)H Mice," 1 J. Nat'l Cancer Inst. 119 (1940)
Summary: DES possesses the same ability as other estrogens to induce mammary cancer in mice.

TABLE A

Publications Regarding the Carcinogenic Properties of Estrogens Such as DES

Hugh Auchinloss and Cushman Haagensen, "Cancer of the Breast Possibly Induced by Estrogenic Substance," 114 J. Am. Med. Ass'n 1517 (1940)
Summary: Four cases of breast cancer in humans from exposure to estrogens.

S. Zuckerman, "The Histogenesis of Tissues Sensitive to Oestrogens," 15 Biol. Rev's Cambridge Phil. Soc. 231 (1940)
Summary: Estrogen stimulates endometrial and metaplasic changes in rats.

1945:
J.S. Henry, "Avoidance of Untoward Effects of Oestrogenic Therapy in Menopause," 53 Canadian Med. Ass'n 31 (1946)
Summary: Notes malignant endometrial changes in humans from estrogen therapy.

1947:
S.B. Gusberg, "Precursors of Corpus Carcinoma Estrogens and Adenomatous Hyperplasia," 54 Am. J. Obstetrics and Gynecology 312 (1947)
Summary: Adenomatus hyperplasia of the endometrium, another malignancy in humans caused by estrogens.

TABLE A

Publications Regarding the Carcinogenic Properties of Estrogens Such as DES

Gordon Rosenblum and Eugene Melinkoff, "Preservation of Threatened Pregnancy With Particular Reference to the Use of Diethylstilbestrol," 55 Western J. of Surgery, Obstetrics, & Gynecology 597 (1947)

Summary: "Can diethylstilbestrol in any way affect the glandular balance of the child *in utero*?"

1948:

O.M. DeVaal, "Experimentally Induced Intersexuality in Mice," 1 Acta Endocrinology 319 (1948)

Summary: Cornification of vaginal tissue in mice caused by estrogens.

1949:

A. Vass, "Occurrence of Uterine Fundus Carcinoma After Prolonged Estrogen Therapy," 58 Am. J. Obstetrics and Gynecology 748 (1949)

Summary: Two cases of cancer of the uterine fundus in humans related to estrogen therapy

TABLE B

Publications Regarding the Ability of Drugs Such as DES to Cross the Placenta and Effect Offspring *In Utero*

1937:
William R. Lyons, "The Hormonal Basis of Witches Milk," 37 Proceedings of the Society for Experimental Biol. and Med. 207 (1937)
Summary: Estrogen given to mother found in placenta and in infant.

1939:
Harold Speert, "The Placental Transmission of Sulfanilamide and its Effects Upon the Fetus and Newborn," 66 Bulletin of Johns Hopkins Hosp. 139 (1939)
Summary: Sulfanilamide given to pregnant rats caused the death of their fetuses.

1945:
L.J. Davis and William Forbes, "Thiouracil in Pregnancy: Effect on Fetal Thyroid," 11 Lancet 740 (1945)
Summary: Fetuses of pregnant rats given Thioracil exhibited same symptoms as adult rats exposed to the drug.

TABLE B

Publications Regarding the Ability of Drugs Such as DES to Cross the Placenta and Effect Offspring *In Utero*

1947:
C.D. Larsen, et al., "Pulmonary-Tumor Induction by Transplacental Exposure to Urethane," 8 J. Nat'l Cancer Inst. 63 (1947)
Summary: Urethane given to pregnant rats caused lung cancer in their offspring.

1948:
L.B. Flexner, et al., "The Permeability of the Human Placenta to Sodium in Normal and Abnormal Pregnancies and the Supply of Sodium to the Human Fetus as Determined With Radioactive Sodium," 55 Am. J. Obstetrics and Gynecology 469 (1948)
Summary: Radioactive sodium given to a pregnant woman is found in the placenta and the fetus.

TABLE C

Publications Regarding the Ability of Drugs Such as DES to Cause Sexual Tract Abnormalities in Those Exposed *In Utero*

1930:
R. Courrier, "Rechereches Sur le Mecanisme de la Crise Genitale du Nouve-Ne," Proceedings of the Second Int'l Congress for Sex Research 353 (1931)
Summary: The offspring of guinea pigs injected with estrone during pregnancy exhibited intersex characteristics.

1939:
R.R. Greene, et al., "Experimental Intersexuality: Modification of Sexual Development of the White Rat with Synthetic Estrogen," 41 Proceedings of the Soc. for Experimental Biol. and Med. 169 (1939)
Summary: DES deformed the sexual organs of female rats exposed to the drug.

R.R. Greene, et al., "Experimental Intersexuality: The Paradoxical Effects of Estrogen on the Sexual Development of the Female Rat," 74 Anatomical Record 429 (1939)
Summary: Estrogens malformed the reproductive systems of female rats.

1944:
R.R. Greene, "Embryology of Sexual Structure and Hermaphroditism," 4 J. Clinical Endocrinology 335 (1944)
Summary: Links hormonal imbalance in mammals to hermaphrodism.

TABLE C

Publications Regarding the Ability of Drugs Such as DES to Cause Sexual Tract Abnormalities in Those Exposed *In Utero*

1947:
Karl J. Karnaky, "Estrogenic Tolerance in Pregnant Women," 53 Am. J. Obstetrics and Gynecology 312 (1947)
Summary: Baby girls exposed to DES *in utero* exhibited darkening of the nipples and labia.

1948:
O.M. DeVaal, "Experimentally Induced Intersexuality in Mice," 1 Acta Endocrinology 319 (1948)
Summary: Estrogens will cause vaginal cornification in mice as well as other urogenital and uterine anomalies.

1950:
Robert K. Enders, et al., "Mink Production in Relation to Stilbestrol," 16 The Fur J. 4 (1950)
Summary: DES given to mink prevented them from producing offspring.

TABLE D

Studies Finding DES of No Use in Preventing Miscarriage

1947:
M.E. Davis and N.W. Fugo, "Effects of Various Sex Hormones on Excretion of Pregnandiol Early in Pregnancy," 65 Proceedings of the Soc. Experimental Biol. and Med. 39 (1947)
Summary: Could not reproduce the reported efficacy of DES; found no benefit from DES administration during pregnancy.

1949:
I.F. Somerville, et al., "Effect of Diethylstilbestrol of Urinary Excretion of Pregnandiol and Endogenous Estrogen During Pregnancy," Lancet, April 23, 1948, at 680
Summary: Found no favorable change in hormonal balance from the prescription of DES during pregnancy.

1950:
Edward M. Davis and Nicholas W. Fugo, "Steroids in the Treatment of Early Pregnancy Complication," 142 J. Am. Med. Ass'n 778 (1950)
Summary: Questioned the value of DES as a miscarriage preventative.

TABLE D

Studies Finding DES of No Use in Preventing Miscarriage

E.D. Colvin, et al., "Salvage Possibilities in Threatened Abortion," 59 Am. J. Obstetrics and Gynecology 1208 (1950)

Summary: Found that prophylactic use of DES was wholly unwarranted and that bed rest and sedation are the only effective treatments of threatened miscarriage.

R.E. Crowder, et al., "The Management of Threatened Abortion: A Study of 100 Cases," 60 Am. J. Obstetrics and Gynecology 896 (1950)

Summary: Found that DES does not stimulate the body to produce new hormones of its own and therefore there is no basis for the use of DES in preventing miscarriage.

Ralph A. Reis, et al., "The Management of the Pregnant Diabetic Woman and Her Newborn Infant," 60 Am. J. Obstetrics and Gynecology 1023 (1950)

Summary: Stated that it was "unnecessary" to subject pregnant women to DES.

1952:

David Robinson and Landrum Shettles, "The Use of Diethylstilbestrol in Threatened Abortion," 63 Am. J. Obstetrics and Gynecology 1330 (1952)

Summary: Complete failure of DES to prevent miscarriage.

TABLE D

Studies Finding DES of No Use in Preventing Miscarriage

Paul Pedowitz and Edmund L. Shievin, "The Pregnant Diabetic," Bulletin of the New York Academy of Medicine 440 (1952)
Summary: Found that substitutional hormonal therapy, such as DES therapy, was not warranted.

1953:
Arthur King, "Threatened and Repeated Abortion: Present Status of Therapy," 1 Obstetrics and Gynecology 104 (1953)
Summary: Analyzed the studies purporting to show that DES was effective; found instead that studies were without adequate controls and did not rule out random chance as the reason for the positive results.

James Henry Ferguson, "The Effect of Stilbestrol on Pregancy Compared to the Effect of a Placebo," 65 Am. J. Obstetrics and Gynecology 592 (1953)
Summary: DES has no effect on fetal survival.

W.J. Dieckmann, et al., "Does the Administration of Diethylstilbestrol During Pregnancy Have Therapeutic Value?" 66 Am. J. Obstetrics and Gynecology 1062 (1953)
Summary: First double-blind, prospective study of DES in preventing miscarriage. DES did not reduce the number of miscarriages.

TABLE D

Studies Finding DES of No Use in Preventing Miscarriage

1955:

Louis Sanford Goodman, et al., The Pharmacological Basis of Therapeutics (2d ed. 1955)

Summary: "Certainly the available evidence does not justify the routine use of estrogen in the treatment of threatened abortion or as a prophylactic against the pregnancy."

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(20)

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WYETH,
Petitioner,
v.
DIANE LEVINE,
Respondent.

On Writ of Certiorari to the
Vermont Supreme Court

BRIEF OF *AMICI CURIAE* FORMER FDA COMMISSIONERS DR. DONALD KENNEDY AND DR. DAVID A. KESSLER IN SUPPORT OF RESPONDENT

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INTEREST OF *AMICI CURIAE*[1]

This brief in support of respondent is filed on behalf of Dr. Donald Kennedy and Dr. David Kessler, each of whom served as Commissioner of Food and Drugs at the Food and Drug Administration (FDA).

Dr. Donald Kennedy, a biologist, served as FDA Commissioner from 1977 to 1979. Dr. Kennedy then returned to Stanford University, where he had previously been a member of the faculty. From 1980 to 1992, Dr. Kennedy served as President of Stanford University. When he stepped down he returned to the faculty and is currently a professor emeritus. From 2000 until 2008, Dr. Kennedy also served as editor-in-chief of *Science*, the weekly magazine published by the American Association for the Advancement of Science.

Dr. David A. Kessler was appointed by President George H.W. Bush in 1990 to serve as FDA Commissioner. Dr. Kessler was reappointed to that position by President William J. Clinton. After serving as Commissioner for seven years, Dr. Kessler left the FDA in 1997 to join the Yale School of Medicine as Dean, a position he held until 2003. From 2003

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[1] Pursuant to Rule 37.6 of the Rules of the Supreme Court of the United States, no counsel for a party authored this brief in whole or in part, and no counsel or party made a monetary contribution intended to fund the preparation or submission of this brief. No person other than *amici curiae* or their counsel made a monetary contribution to its preparation or submission. The parties have consented to the filing of this brief.

through 2007, Dr. Kessler served as Dean and Vice-Chancellor of the University of California, San Francisco, Medical School. Dr. Kessler remains on the medical school faculty.

Amici file this brief because the pro-preemption position urged by petitioner and the United States threatens to undermine, not advance, the underlying goal of our nation's drug safety laws, which is "to protect consumers from dangerous products." *United States v. Sullivan*, 332 U.S. 689, 696 (1948); *see also United States v. Dotterweich*, 320 U.S. 277, 282 (1943). The nation's drug safety laws have never placed the responsibility for drug safety solely on FDA. To the contrary, they place primary responsibility for safety squarely on the shoulders of drug manufacturers. To be sure, FDA also plays an important role; it oversees, and when necessary compels, compliance with safety standards. But the ultimate responsibility remains with the manufacturer. *Amici* submit that the pro-preemption arguments pressed by petitioner and the United States turn that understanding upside down, relieving manufacturers of front-line responsibility for the safety of their drugs and handing that job to the FDA.

Failure-to-warn litigation has always played an important role in ensuring that manufacturers bear responsibility for the safety of their drugs. Failure-to-warn litigation preceded the enactment of the first federal drug safety law, the Federal Pure Food and Drug Act of 1906, and it has been a complement to federal enforcement of drug safety laws throughout the history of FDA and its predecessor agencies. Indeed,

until 2002, failure-to-warn litigation was seen by both Congress and FDA as an important adjunct to federal regulation.

Congress has been particularly attentive to the federalism issues relating to FDA regulation of drugs and medical devices, but has never seen fit to preempt state failure-to-warn claims for drugs. Congress has, over the years, provided limited preemption of state-law claims for medical devices specifically approved by FDA, over-the-counter drugs, and vaccines. Although Congress has repeatedly revisited the Federal Food, Drug, and Cosmetic Act of 1938 (FDCA), including a significant overhaul in the 2007 Food and Drug Administration Amendments Act, Congress has never given drug companies the immunity from liability they covet and now seek from this Court.

Congress's unwillingness to cut off state failure-to-warn litigation is in keeping with FDA's longstanding judgment that this litigation complements the agency's regulatory and enforcement activities. At least until 2002, FDA consistently took the position that state failure-to-warn litigation enhances consumer safety by serving three critical functions:

* **Information:** State failure-to warn litigation augments the FDA's post-approval surveillance of drug safety by uncovering hazards unknown to FDA and by providing information about those hazards to the agency, physicians and patients;

* **Incentives:** State failure-to-warn litigation provides powerful incentives for drug companies to

disclose safety risks with their products to FDA, physicians and patients as soon as evidence of a serious hazard becomes available; and

* **Compensation:** State failure-to-warn litigation serves a compensatory justice function unaddressed by federal law (except for vaccines).

For these reasons, *amici* submit that the absence of a robust system of state failure-to-warn litigation would severely compromise FDA's ability "to protect consumers from dangerous products." Both Dr. Kennedy and Dr. Kessler have set forth their views on this topic; Dr. Kennedy in an editorial, *Misbegotten Preemptions*, 320 Science 585 (May 2, 2008), and Dr. Kessler in a law review article, David A. Kessler & David C. Vladeck, *A Critical Examination of the FDA's Effort to Preempt Failure-to-Warn Claims*, 96 Geo. L.J. 461 (2008) (hereinafter Kessler & Vladeck).

SUMMARY OF ARGUMENT

Troubled by the public health implications of petitioner's and the United States' positions in this case, *amici* file this brief to amplify three points that may not stand out in respondent's more comprehensive treatment of the issues:

First, there is no conflict between federal and state law over the contents of a drug's label, or a manufacturer's duty to warn physicians, patients, and FDA of emerging safety hazards. To be sure, the FDCA gives FDA substantial authority over the labeling and promotion of pharmaceutical products.

But nothing in the FDCA, or in FDA's implementing regulations, relieves a manufacturer of its duty to warn physicians and patients of emerging safety risks as soon as that information becomes available. This duty predates by decades the advent of federal regulation of drugs. *See, e.g., Thomas v. Winchester*, 6 N.Y. 397 (1852). FDA's longstanding regulations make clear that a drug company has a duty to modify labeling without delay when hazards emerge with one of its drugs. The regulations expressly authorize the company to make labeling changes, and take other steps to inform physicians and patients of emerging risks, without advance approval from the agency.

Moreover, failure-to-warn litigation does not challenge *FDA's* decisions about labels; rather, it challenges a *company*'s failure to alert physicians and patients to risks that were unknown or poorly understood when FDA approved the drug's label, but were evident to the company at the time the plaintiff sustained injury. Litigation of that sort complements, not undercuts, FDA's job of protecting consumers from dangerous drugs.

Second, petitioner's argument depends on two related myths: *first*, that FDA has timely access to safety information and to resources that enable it to engage in the day-by-day monitoring of the safety profile of all of the thousands of drugs on the market; and *second*, that FDA's capacity to keep abreast of emerging safety information — even after a drug moves from pre-approval clinical testing to post-approval use in thousands or millions of patients — is equal to that of the drug's manufacturer. Neither of

these myths is true today; neither was true when Dr. Kennedy and Dr. Kessler headed FDA; and neither will be true tomorrow. The simple fact is that drug companies have far superior information-gathering tools about the safety profile of the drugs they sell, while FDA's tools to keep track of safety hazards post-approval are imperfect at best. For this reason, FDA has always imposed a duty on manufacturers that parallels and reinforces the same duty state law imposes — namely, the duty to disclose emerging safety information to FDA and physicians as soon as it becomes available. Contrary to petitioner's claim, there is no tension between federal and state law; the requirements imposed by federal regulations and state duty-to-warn laws are parallel in all material respects.

Third, the background history of state failure-to-warn litigation over drug products, coupled with Congress's unwillingness to include an express preemption provision in the drug provisions of the FDCA, counsel strongly against finding implied preemption in this case. Congress's refusal to give the pharmaceutical industry the liability protection it covets reflects Congress's judgment that, whatever tensions might theoretically exist between the FDCA and application of state law, the benefits to consumer protection derived from state failure-to-warn litigation exceed the costs. Leaving Congress's decision undisturbed makes particular sense here, where petitioner's and FDA's claims of conflict between state and federal law are not based on hard evidence of actual conflict but instead rest only on predictive judgments unanchored to history.

ARGUMENT

I. State Failure-to-Warn Litigation Does Not Conflict With FDA's Authority Over Drug Labeling.

Petitioner's implied preemption argument rests on the false premise that failure-to-warn litigation seeks to supplant FDA as final decision-maker as to the content of drug labeling. That is not so. The FDCA gives FDA substantial authority over drug labeling. 21 U.S.C. § 355(d). Failure-to-warn litigation does not undercut FDA's authority over drug labeling; rather, it challenges the *company's* failure to warn doctors and patients about risks that were unknown or poorly understood at the time FDA approved the drug and the label, but were evident to the company at the time the plaintiff sustained injury.

The emergence of safety hazards that were unknown or not well understood at the time of a drug's approval is commonplace. FDA's approval process is not a warrant of the drug's absolute safety, but is an assessment of whether the drug's benefits outweigh its potential risks based on the evidence available to FDA at the time.

To obtain approval for a new drug, a manufacturer must submit a new drug application (NDA) for the agency's review. 21 U.S.C. § 355; *see generally* Kessler & Vladeck, 96 Geo. L.J. 470-73. The NDA must include, among other things, full results of all clinical studies performed on human subjects. Pre-market human studies generally involve only a few thousand

subjects and last only a year or so. To control for conditions that might distort the study's findings, subjects who take other drugs or have other diseases or infirmities are excluded. *See* Kessler & Vladeck, 96 Geo. L.J. at 471. Because of these limitations, pre-approval testing is generally incapable of detecting adverse effects that have long latency periods, result from drug interactions, occur infrequently, or affect sub-populations excluded from or not adequately represented in the clinical studies (for example, the elderly, ethnic minorities, and pregnant women). *Id.* Moreover, FDA's assessment of risks-versus-benefits is generally done population-wide, not sub-group by sub-group, because there are rarely enough clinical trial participants in a sub-group to permit that degree of refined analysis. *Id.* For these reasons, FDA approval of a drug is no guarantee that the drug will not cause serious adverse effects even if properly used for its approved purposes.[2]

When FDA approves a new drug, it also approves the precise final version of the drug's label. 21 U.S.C. § 355(b)(1)(F). Because the NDA process is intended to provide FDA with all then-existing information about the drug's risks, the label approved by the FDA represents the agency's best judgment about risks that warrant disclosure and those that do not.

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[2] Professor and former FDA General Counsel Richard A. Merrill once quipped, "All consumers of prescription drugs serve as guinea pigs for the pharmaceutical industry." *Compensation for Prescription Drug Injuries*, 59 Va. L. Rev. 1, 20 (1973).

But the label's content is not set in stone. Once a drug enters the marketplace, unanticipated adverse effects begin to emerge and the drug's labeling needs to be revised. Generally labeling changes are initiated by the manufacturer and subject to FDA pre-approval. 21 C.F.R. § 314.70(b). But there are exceptions. The most important exception is that "labeling *shall* be revised to include a warning as soon as there is reasonable evidence of an association of a serious hazard with a drug[.]" 21 C.F.R. § 201.80(e) (emphasis added); *see also id.* § 201.57(c)(6)(i) (imposing requirement in slightly different language). Statements that may be added to labels without prior FDA approval are those:

> [A] To add or strengthen a contraindication or warning, precaution, or adverse reaction; [B] To add or strengthen a statement about drug abuse, dependence, psychological effect, or overdosage; [C] To add or strengthen an instruction about dosage and administration that is intended to increase the safe use of the product; [or D] To delete false, misleading, or unsupported indications for use or claims of effectiveness.

21 C.F.R. § 314.70(c)(6)(iii)(A)-(D).

Once a manufacturer adds a warning, it must then promptly inform FDA of the change being effected (or CBE) in a supplemental NDA, which FDA reviews after-the-fact. *Id.* § 314.70(c). This "safety valve" option enables a manufacturer to provide physicians, health care professionals, and patients up-to-date safety information without the need to secure FDA's

advance approval. And FDA has long made clear that its labeling rules are no obstacle to a manufacturer providing safety information to doctors and patients though labeling, advertising, "Dear Doctor" letters, and other avenues of communication as soon as the manufacturer discovers risks not mentioned on the label. 44 Fed. Reg. 37,434, 37,447 (June 26, 1979); 30 Fed. Reg. 993 (Jan. 30, 1965).[3]

As noted, failure-to-warn litigation does not challenge FDA's authority over drug labeling, but instead challenges a company's failure to take measures to notify physicians and patients when safety problems emerge with a drug. These cases seek money damages for injuries caused by a lack of an adequate warning, not injunctions or other court decrees to force labeling changes.[4]

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[3] Although petitioner focuses on labeling, failure-to-warn cases typically challenge the drug company's failure to *warn*, not failure to revise *labeling*. A drug company can discharge its duty to warn through other means, including, for example, "Dear Doctor" letters, information distributed by the company's sales-force, advertising and promotional materials, and other communications with doctors and patients. *See, e.g., In re Zyprexa Products Liability Litigation*, 489 F.Supp. 2d 230, 248-60 (E.D.N.Y. 2007) (considering but rejecting company's defense that prescribing physicians knew of the link between Zyprexa and diabetes from the company's sales representatives even before association appeared on the drug's label).

[4] Prior to 2002, FDA repeatedly made clear that

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In failure-to-warn litigation, the plaintiff alleges that the drug company failed adequately to warn of risks that were evident to the company, but undisclosed, at the time the plaintiff was injured. Almost invariably, the risks at issue were unknown or poorly understood at the time FDA approved the drug and its label.[5] In a typical case, a judgment in the plaintiff's favor may result in the company deciding

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[4](...continued)
agency labeling decisions did not preempt tort liability. *See, e.g.*, 44 Fed. Reg. at 37,447 (FDA labeling decisions do not "influence civil tort liability of the manufacturer."); 59 Fed Reg. 3,944, 3,948 (Jan. 27, 1994) (recognizing that "product liability plays an important role in consumer protection," in notice proposing rules to protect the identities of individuals reporting adverse drug reactions); 63 Fed. Reg. 66,378, 66,384 (Dec. 1, 1998) (observing that FDA labeling "regulations establish the minimal standards necessary, but were not intended to preclude the states from imposing additional labeling requirements," in FDA's final guidance on prescription drug labeling).

[5] Many of the recent failure-to-warn cases, including those involving Vioxx, Ortho Evra, Propulsid, Zyprexa, and Avandia, allege that the drug's manufacturer withheld important safety data from FDA. *See infra* n.11. The Vioxx cases underscore that FDA did not understand the cardiovascular risks posed by the drug at the time of approval and that Merck withheld information relating to the drug's cardiovascular risks from FDA to avoid a stronger warning on the label. *See* Thomas O. McGarity, *The Preemption War* 1-17 (Yale Univ. Press 2008) (detailing Vioxx's regulatory history); *McDarby v. Merck*, 949 A.2d 223, 231-47 (N.J. App. Div. 2008) (same).

that the risk is sufficiently common or grave to warrant a warning. The company would then ask FDA to approve a warning change or add a warning to the label and then seek FDA's approval. It is also possible that, regardless of the case's outcome, safety information disclosed as a result of the litigation might prompt FDA to decide that a stronger warning is appropriate and to initiate discussions with the company over a labeling change. *See Bates v. Dow Agrosciences, LLC*, 544 U.S. 431, 451 (2005) (observing that state damages litigation "may aid in the exposure of new dangers associated with" the product and prompt the agency to "decide that revised labels are required in light of the new information that has been brought to its attention.").[6]

Notwithstanding Wyeth's efforts to paint this case otherwise, this is a garden variety failure-to-warn case. Diana Levine's injury was caused by the intravenous administration of Wyeth's drug Phenergan through the "direct IV" or "IV push" method, whereby Phenergan is supposed to be injected directly into the patient's *vein*, but was instead injected into her *artery*. *Levine v. Wyeth*, 2006 VT 107 (2006). The evidence showed that Wyeth had known for decades that the IV push method of administration can result in inadvertent contact

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[6] This happens with some regularity with respect to drug labeling. *See, e.g.*, Aaron Kesselheim & Jerry Avorn, *The Role of Litigation in Defining Drug Risks*, 297 JAMA 308, 310 (2007) (citing examples); David B. Ross, *The FDA and the Case of Ketek*, 356 New Eng. J. of Med. 1601 (2007).

between the drug and the patient's artery. When the drug comes in contact with an artery, the artery can die and necrosis, gangrene and amputation can result. Ms. Levine was forced to have her arm amputated due to the administration of Phenergan through the IV push method. *Id.* at ¶2. The evidence showed that Wyeth failed to instruct physicians not to use push IV, either in its labeling or otherwise. *Id.* at ¶3. Indeed, Wyeth argued that adding the warning Ms. Levine claimed was lacking — an explicit direction to physicians not to use IV push — "would have harmed patients by eliminating the IV push as an option for administering Phenergan." *Id.* at ¶23; *see also id.* at ¶3.

To be sure, Wyeth argues that implied preemption is warranted here because the FDA considered and rejected the specific warning Ms. Levine claims was lacking. But both the trial court and the Vermont Supreme Court rejected that argument as a matter of fact. *Id.* at ¶¶21-23. The Vermont Supreme Court acknowledged that, during the over fifty years that Phenergan has been approved for use, Wyeth and FDA twice discussed modifications to the label. *Id.* But the Vermont Supreme Court found no evidence that (a) FDA had ever considered and approved the safety of the IV push method of administration, (b) FDA had determined that Ms. Levine's claim was scientifically unsubstantiated, (c) FDA intended to prohibit Wyeth from strengthening its label to warn physicians against using the IV push method, or (d) FDA made an affirmative decision to preserve the IV push method of administration. *Id.* at ¶23. Wyeth's arguments to the contrary are not based on the record.

Wyeth's efforts to obscure the real facts of this case are not surprising. The reality is that few, if any, cases fall into the fact pattern that Wyeth alleges occurred here. Neither Wyeth nor the United States point to any actual man-bites-dog cases where a company (which is trying to sell its drug) wants a *stronger* label than FDA does, and FDA (which is trying to safeguard the public health) *resists* the change.[7] In case after

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[7] Even if such a case arose, the company still may strengthen its label if, in its view, a stronger warning is warranted. As one court recently noted, "Although the FDA might later disapprove of a label strengthened pursuant to 21 C.F.R. § 314.70(c) and § 201.80, the FDA's power to disapprove does not make the manufacturer's voluntarily strengthened label a violation of federal law." *Tucker v. SmithKline Beecham Corp.*, 2008 U.S. Dist. LEXIS 55919 * 8 (S.D. Ind. 2008) (citations omitted). After all, "FDA might do nothing, thus giving effect to the change." *Id.* Even if FDA disapproves the revised label, "the FDA's disapproval is not retroactive[]" and the manufacturer may remove the warning. *Id.; see also* 21 C.F.R. § 314.70(c)(7). In such a case, the manufacturer would have an airtight regulatory compliance defense in a tort suit, but if the company never seeks to change the label, it should not be able to use the approval requirement as a liability shield. And if the manufacturer retains the label even after FDA's disapproval, FDA can, in theory, bring a "misbranding" action in court, and a jury would decide the question. *Tucker*, at * 8 & n.3; 21 U.S.C. § 352(a), (f), (j). To *amici*'s knowledge, FDA has never brought a misbranding action under these circumstances. *Cf. Feldman v. Lederle Labs.*, 592 A.2d 1176, 1193 (N.J. 1991) ("for the FDA to have prevented a drug manufacturer from warning the public of

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case, companies *fight* stronger warnings that might discourage doctors from prescribing their drugs and thereby undermine the drugs' profitability.[8] For instance, it took FDA over a year to force Merck, the manufacturer of Vioxx, to add a statement about Vioxx's cardiovascular risks to the drug's label. Merck fought hard because it had determined that a "warning" rather than a "precaution" on Vioxx's label could lead to a 50% reduction in Vioxx's sales.[9] During the year-long negotiations between Merck and FDA, no change was made to Vioxx's label, and in the end, the FDA accepted a compromise: The statement about cardiovascular risk was added to the "precaution"

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a newly-discovered danger . . . 'would seem anomalous.'") (citation omitted).

[8] *See, e.g.*, Kessler & Vladeck, 96 Geo. L. J. at 480 (and authorities cited therein); *McDarby v. Merck*, 949 A.2d at 238-48 (account of dispute between Merck and FDA over Vioxx's label); *In re Vioxx Products Liability Litigation*, 501 F. Supp. 2d 776, 779, 783 (E.D. La. 2007) (same); Margaret A. Berger & Aaron D. Twerski, *From the Wrong End of a Telescope: A Response to Professor David Bernstein*, 104 Mich. L. Rev. 1983, 1987-88 (2006) (recounting Sandoz's effort to avoid labeling changes for its lactation-suppressing drug Parlodel, which it ultimately withdrew from the market).

[9] *McDarby v. Merck*, 949 A.2d at 241. *See also* Alex Berenson, *Eli Lilly Said to Play Down Risk of Top Pill*, N.Y. Times, Dec. 17, 2006, at A1 (discussing Eli Lilly's effort to avoid a warning on Zyprexa, its best selling schizophrenia medication, for diabetes risk).

section of the label as Merck urged, not to the "warning" section, notwithstanding FDA's judgment that a warning was appropriate. *See* Kessler & Vladeck, 96 Geo. L.J. at 480 & n.82 (citing congressional testimony of FDA officials acknowledging that FDA did not have the power to compel Merck to add a warning to Vioxx's label).[10]

As is clear, contrary to the submissions of petitioner and the United States, there is no conflict between the application of state failure-to-warn litigation and FDA's authority over drug labeling. These regimes have co-existed without friction for the entire life-span of the agency. Nothing in this case or in the reasoned decision of the Vermont Supreme Court threatens FDA's ability to control drug labeling. For that reason the judgment below should be affirmed.

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[10] The 2007 Amendments to the FDCA give FDA, for the first time, the authority to compel a manufacturer to add warnings to a drug's label. 21 U.S.C. § 505(o)(4). Even so, this power is significantly circumscribed and cannot, as an ordinary matter, be used by the agency unilaterally or immediately. FDA may "accelerate" the process when "a labeling change is necessary to protect the public health." But the agency may not bypass the process set up in the Act. *Id.* at § 505(o)(4)(H); *See also* Kessler & Vladeck, 96 Geo. L. J. at 467-68 n.24.

II. FDA's Post-Approval Monitoring System Cannot, On Its Own, Adequately Safeguard Public Health.

The pro-preemption arguments advanced by petitioner and the United States fail for another reason: They significantly overstate FDA's ability to police the marketplace on its own, without the backstop of state failure-to-warn litigation. The question before this Court is whether state failure-to-warn litigation jeopardizes the fulfillment of the FDCA's goal, namely, "to protect consumers from dangerous products." *United States v. Sullivan*, 332 U.S. at 696.

The short answer to that question is "no." State failure-to-warn litigation plays an indispensable role in achieving that goal. The fundamental problem FDA faces is that, by necessity, drugs are approved on the basis of less-than-perfect knowledge. Risks that are rare, have long latency periods, result from drug interactions, or have adverse impacts on sub-populations often go undetected in clinical testing. Despite FDA's recent claims, the agency cannot single-handedly perform the Herculean job of monitoring the safety of every one of the 11,000 or so drugs on the market. Until 2002, FDA recognized that failure-to-warn litigation served as an important backstop to the agency's own efforts. *See* Kessler & Vladeck, 96 Geo. L.J. at 483-86.

Nonetheless, petitioner and the United States paint a portrait of FDA that is unrealistic. Contrary to their claims, FDA does not have timely access to safety

information and other resources to enable it to engage in a day-by-day monitoring of the safety profile of every one of the thousands of drugs on the market (not to mention medical devices, food products, blood products and other biologics, and the hundreds of other consumer products FDA regulates), let alone the capacity to monitor the safety profile of an individual drug that is even remotely equivalent to that of the drug's manufacturer. *Id.* There are several reasons why the Court should be skeptical of petitioner's and the United States' arguments about FDA's ability to police the market on its own.

First, these arguments are called into doubt by recent history. In the past few years, FDA has faced a flood of high-profile regulatory failures with recently approved drugs, including pain medications Vioxx, Celebrex, and Bextra, the diabetes drugs Avandia and Rezulin, and the heartburn drug Propulsid. In each of these cases, there was a substantial delay between when the manufacturer had "reasonable evidence of an association of a serious hazard" with its drug (*see* 21 C.F.R. §§ 201.57(c)(6)(i), 201.80(e)), and when the manufacturer provided that information to FDA or took action to warn physicians or patients. *See id.* (a manufacturer *shall* revise labeling once it has reasonable evidence of an association).[11]

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[11] *See, e.g., Darby v. Merck*, 949 A.2d at 241-44 (pointing out Merck's delays in reporting information about Vioxx's cardiovascular risks to FDA); Alex Berenson & Gardiner Harris, *Pfizer Says 1999 Trials Revealed Risks With Celebrex*. N.Y. Times, Feb. 1, 2005, A1 (reporting that

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Second, FDA's post-approval surveillance resources do not match FDA's rhetoric. Both the Institute of Medicine (IOM) and the Government Accountability Office (GAO) have issued reports highly critical of FDA's surveillance programs, with the IOM concluding that the programs detect at most a "small fraction of all adverse effects of drugs."[12] Detection is

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Pfizer acknowledged withholding from FDA for two years study showing serious cardiovascular risk with Celebrex); Gardiner Harris and Eric Koli, *Lucrative Drug, Danger Signals and the FDA*, N.Y. Times, June 10, 2005 (discussing delays in reporting safety information on heartburn medication Propulsid); Denise Grady, *FDA Reviews Accusations About Diabetes Drug*, N.Y, Times, Mar. 16, 2000 (reporting that FDA records showed that company failed to submit safety data on diabetes drug Rezulin); Gardiner Harris & Alex Berenson, *Drug Makers Near Old Goal: A Legal Shield*, N.Y. Times, Apr. 6, 2008, A1 (reporting that documents obtained during litigation showed that Johnson & Johnson delayed informing the FDA for years that Ortho Evra, a birth control patch, delivered far more estrogen than it claimed, increasing the risks of blood clots and strokes, and noting that "[i]n the last decade, suits over Zyprexa, the withdrawn pain pill Vioxx, the withdrawn diabetes medicine Rezulin, the withdrawn heartburn medicine Propulsid and several antidepressants have shown that companies played down the risks of their medicines.").

[12] IOM, *The Future of Drug Safety, Promoting and Protecting the Health of the Public* 51, 53 (2006) (hereinafter "IOM Report"); GAO, *Drug Safety: Improvement Needed in*
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not the only problem. As the IOM put it, "[t]he existing regulatory framework is structured around the premarketing testing process; few tools are available for addressing postmarketing issues, short of the blunt instruments available to respond to clear-cut adulteration and misbranding." IOM Report at 153. Even if these programs are strengthened, top down FDA surveillance is no substitute for failure-to-warn litigation, which provides FDA, doctors and patients with safety information that is otherwise unavailable to the agency.

Third, petitioner's argument assumes that FDA and a drug manufacturer have equal access to information about emerging safety hazards with the manufacturer's drug. That is not the case. Manufacturers have superior resources that are committed to overseeing the safety of the drugs they market. As a result, manufacturers invariably get safety information before the FDA does and have access to information that is not available to FDA.

This fact should not be surprising. Drug companies have dedicated sales forces (detailmen) who visit with doctors quite frequently (weekly or, at times, more

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FDA's Postmarket Decision-Making and Oversight Process 18 (2006) (hereinafter "GAO Drug Safety"). Although the 2007 Amendments bolster FDA's authority in this area, the reforms available under the Amendments will take considerable time to implement and their success is uncertain. Kessler & Vladeck, 96 Geo. L.J. at 489-91.

often). Detailmen serve as an early warning system when problems begin to emerge with a drug and as a means by which drug companies disseminate risk information to doctors.[13] Drug companies also sponsor trials of approved drugs to see if they are effective for new uses not approved by the FDA. For instance, a study on Vioxx in Alzheimer's patients showed a higher incidence of cardiovascular events than did the placebo group, but Merck did not disclose the study's results to

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[13] There are an estimated 90,000 drug company sales representatives (detailmen) in the United States. *See, e.g.*, Stephanie Saul, *Gimme an Rx! Cheerleaders Pep Up Drug Sales*, N.Y. Times, Nov. 28, 2005, A1; Stephanie Saul, *Drug Makes Pay for Lunch as they Pitch*, N.Y. Times, July 28, 2006, A1; Stephanie Saul, *Doctor Says Drug Maker Tried to Quash His Criticism of Avandia*, N.Y. Times, June 7, 2007, A1 (reporting that FDA reprimanded Glaxo, the manufacturer of Avandia, for having its detailmen play down drug's risks to doctors); Alex Berenson, *Drug Files Show Maker Promoted Unapproved Use*, N.Y. Times, Dec. 18, 2006, A1 (reporting that Eli Lilly detailmen promoted Zyprexa, a powerful drug for schizophrenia and bipolar disorder, for patients who had neither illness). GAO reports that FDA lacks the resources to police effectively drug company promotional efforts. GAO, *Prescription Drugs: FDA Oversight of the Promotion of Drugs for Off-Label Uses* 6, 9, 24-26, 41-46 (July 2008). The role of detailmen has been pivotal in some failure-to-warn cases. *See, e.g., In re Zyprexa Products Liability Litigation*, 489 F. Supp. 2d at 248-60; *Tatum v. Schering Corp.*, 795 F.2d 925 (11th Cir. 1986); *McDarby v. Merck*, 949 A.2d at 248-49.

FDA for over a year.[14] And drug companies have physicians on staff or contract with physicians to evaluate the safety profile of drugs, but these evaluations are not generally shared with FDA.[15]

Thus, although each drug company has an obligation to report evidence of safety problems in patients treated with a drug, *see, e.g.*, 21 C.F.R. §§ 310.305; 312.32(d)(3), there is no corresponding obligation to report the impression of company doctors and scientists, who generally know more about the company's drug and the risks it might pose than their counterparts at the FDA. For these reasons, failure-to-warn litigation has time and again uncovered safety information that was known to the drug company but not provided to, or otherwise available to, FDA. Kessler & Vladeck, 96 Geo. L.J. 491-95 (and authorities cited therein).

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[14] *McDarby v. Merck*, 949 A.2d at 241.

[15] *See, e.g.*, Daniel Carlat, Op-Ed, *Diagnosis: Conflict of Interest*, N.Y. Times, June 13, 2007, at A21 (explaining that "[b]ecause pharmaceutical companies set much of the agenda for what doctors learn about drugs, crucial information about potential drug dangers is played down, to the detriment of patient care.") (discussing Avandia and Vioxx as examples); Alex Berenson, *Eli Lilly Said to Play Down Risk of Top Pill*, N.Y. Times, Dec. 17, 2006, A1 (reporting that emails and memos from Eli Lilly's top doctors and managers, discovered in litigation, show company's effort to play down the risk of diabetes with its blockbuster drug Zyprexa).

Fourth, even with the 2007 Amendments, the FDA faces a daunting future. A report issued in November 2007 by a blue-ribbon panel appointed by FDA concluded, "The scientific demands on the Agency far exceed its capacity to respond. This imbalance is imposing a significant risk to the integrity of the . . . regulatory system, and hence to the safety of the public." FDA Science Board, *FDA Science and Mission at Risk*: A Report of the Subcommittee on Science and Technology § 1.1 (2007) (hereinafter "FDA Science and Mission at Risk"). This conclusion echoes that of IOM, which warned that FDA "lacks the resources to accomplish its large and complex mission today, let alone to position itself for an increasingly challenging future." IOM Report at 193.

As FDA's panel observed, the agency has enormous and growing responsibilities, but Congress has essentially flat-lined its appropriations. When the FDCA was enacted in 1938, Congress gave FDA a mandate "to review and approve prior to marketing, the safety of color additives, human food additives and animal feed additives, as well as to review and approve the safety and effectiveness of new human drugs, new animal drugs, human biological products and medical devices for human use." FDA Science and Mission at Risk, § 2.1. Since 1938, Congress has enacted "125 statutes that directly impact FDA's regulatory responsibilities," by requiring "the development of implementing regulations, guidance or other types of policy, and some require the establishment of entire new regulatory programs. Virtually all require some

type of scientific knowledge or expertise for the agency to address them." *Id.*

Despite the addition of all of these requirements, Congress did not provide "an appropriation of new personnel and increased funding designed to allow adequate implementation." *Id.* Indeed, during the past two decades, the agency's funding and staffing levels have remained static. For these and other reasons, the report concludes that "[t]his reality, combined with a burgeoning industry . . . has made it increasingly impossible for the FDA to maintain its historic public health mission." *Id.; see also id.* Appendix B, Peter Barton Hutt, *The State of Science at the Food and Drug Administration*, at B-24 – B-34.

Each of these factors undercuts the claim that FDA can, on its own, single-handedly police the safety of every drug on the market. Taken together, these factors underscore *amici*'s concern that finding state failure-to-warn cases preempted would deprive FDA of important safety information and would remove existing incentives that press drug companies to report and promptly respond to emerging safety hazards. For this reason too, the judgment below should be affirmed.

III. Congress's Refusal To Preempt Failure-To-Warn Claims Counsels Against Finding Implied Preemption.

The history of the evolution of the drug safety laws in the United States casts further doubt on petitioner's and the United States' implied preemption arguments.

After all, failure-to-warn litigation has been a constant feature of personal injury litigation in the courts of the United States since the mid-Nineteenth Century. One of the early drug liability cases, *Thomas v. Winchester*, 6 N.Y. 397, dates back to 1852. Since that time, there has been a steady procession of failure-to-warn cases involving drug products.[16]

Congress of course is presumed to have been aware of this litigation when it enacted the Federal Pure Food and Drugs Act of 1906, when it enacted the FDCA in 1938, and when it made major amendments to the FDCA in 1962, 1997 and 2007. *See, e.g., Bates*, 544 U.S. at 449-450; *Bonito Boats, Inc. v. Thunder Craft Boats, Inc.*, 489 U.S. 141, 166-67 (1989).

But there is no need for guesswork about Congress's judgment about the federalism questions relating to pharmaceutical products. There are no fewer than

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[16] *See, e.g., Brunswig v. White*, 8 S.W. 85 (Tex. 1888); *Blood Balm v. Cooper*, 10 S.E. 118 (Ga. 1889); *cf. Howes v. Rose*, 42 N.E. 303 (Ind. App. 1895). After the passage of the 1906 Act, failure-to-warn litigation continued in the courts. *See, e.g., Moehlenbrock v. Parke, Davis & Co.*, 169 N.W. 541 (Minn. 1918); *Valmas Drug Co. v. Smoots*, 269 F. 356 (6th Cir. 1920); *Henry v. Judge & Dolph Drug Co.*, 245 S.W. 358 (Mo. Ct. App. 1922); *Campbell v. Stamper Drug Co.*, 277 P. 770 (Colo. 1929); *Halloran v. Parke, Davis & Co.*, 245 A.D. 727 (N.Y. App. Div. 1935); *Wright v. Carter Products*, 244 F.2d 53 (2d Cir. 1957); *Parke-Davis & Co. v. Stromsodt*, 411 F.2d 1390, 1402 (8th Cir. 1969).

three express preemption provisions that reflect Congress's attention to the federalism issue.

One of these provisions — the preemption provision of the Medical Device Amendments of 1976, 21 U.S.C. § 360k — has been the subject of two recent decisions by this Court. *Riegel v. Medtronic, Inc.*, 128 S. Ct. 999 (2008), and *Medtronic, Inc. v. Lohr*, 518 U.S. 470 (1996).

Another statute, The National Childhood Vaccine Injury Act of 1986, 42 U.S.C. §§ 300aa-1, *et seq.*, was enacted by Congress to provide a means of resolving claims of injury as a result of vaccine administration that was less costly and more expeditious than conventional tort litigation. The Vaccine Injury Act requires that certain claims first be brought before the Vaccine Court, but permits the claimant to pursue tort litigation if disappointed with the Vaccine Court's disposition. *See generally Schafer v. American Cyanamid Co.*, 20 F.3d 1 (1st Cir. 1994) (Breyer, J.) (describing background and operation of the Act).[17]

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[17] The Vaccine Act also shows that Congress did not intend to curtail tort remedies for those injured by unsafe drugs and vaccines. Congress could have preempted vaccine claims, but instead carved them out of the general tort system, and included a back-end opt out for claimants who think that they can do better in the tort system. The Vaccine Act also demonstrates that the FDCA provides injured parties no compensatory remedies. To be sure, the FDA has brought at least one misbranding action for an

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A third provision, added by Congress in 1997 in the Food and Drug Administration Modernization Act, preempts state labeling requirements for non-prescription drugs that are "different from or in addition to" those imposed by the FDCA. The provision goes on to say that it shall not be "construed to modify or otherwise affect the liability of any person under the product liability law of any State." 21 U.S.C. § 379r(a), (e).

Congress has never seen fit to enact a preemption provision with respect to drugs. Indeed, Congress twice has explicitly declined to do so. First, in the 1962 amendments to the FDCA, which require FDA to ensure that a drug is effective as well as safe before the drug is approved, Congress made clear its intent not to preempt claims relying on state common law: "Nothing in the amendments . . . shall be construed as invalidating any provision of State law which would be valid in the absence of such amendments unless there is a direct and positive conflict between such amendments and such provision of State law." Drug

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[17](...continued)
injunction and restitution against companies selling an *unapproved* drug, but the only remedy available for injured consumers is the reimbursement of the modest sums they paid for the unapproved product; tort damages are not available. *United States v. Lane Labs-USA, Inc.*, 427 F.3d 219, 231 (3d Cir. 2005) (upholding restitution order against companies selling shark cartilage as cancer remedy).

Amendments of 1962, Pub. L. 87-781, § 202, 76 Stat. 780, 793.[18]

When Congress revisited the FDCA in 2007, drug companies hoped that it would add an express preemption provision barring tort litigation. Congress did not do so. To the contrary, Congress adopted a "rule of construction" that establishes that FDA's new authority to compel companies to make labeling changes does not alter a manufacturer's obligation "to maintain its label in accordance with existing requirements, including subpart B of part 201 and sections 314.70 and 601.12 of title 21, Code of Federal Regulations (or any successor regulations)." 21 U.S.C. § 355(o)(4)(I). The references to the Code of Federal Regulation are to regulations that mandate that drug companies *shall* revise a drug's label to include a warning as soon as there is reasonable evidence of an association of a serious hazard with the drug, and may do so without FDA's advance approval. *See* 21 C.F.R. §§ 201.57(c)(6)(i); 201.80(e); 314.70; and 601.12. This

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[18] The provision's language underscores Congress's judgment not to displace state product liability law, but to preserve it. *See California Federal Sav. & Loan Ass'n v. Guerra*, 479 U.S. 272, 283 n.12 (1987) (explaining anti-preemption thrust of phrase "a direct and positive conflict"); *Swift & Co. v. Wickham*, 382 U.S. 111, 132 n.3 (1965) (Douglas, J., dissenting) (same). The provision explicitly displaces *only* positive state law *only* where there is "a direct and positive conflict" between the FDCA's new effectiveness requirements and state law. Congress refrained from using broader language that might encompass other state law requirements, such as tort law.

"rule of construction" was added by the House to "clarify that nothing in this legislation or in current law is intended to preempt remedies for consumers injured by dangerous drugs." H.R. Rep. No. 110-225, at 197 (2007); *see also* 153 Cong. Rec. S11,831-34 (Sept. 20, 2007) (statement of Sen. Kennedy); *id.* at S11,834 (statement of Sen. Leahy); *id.* at S11,835 (statement of Sen. Durbin). The provision did not sit well with Members of Congress who wanted to add a preemption provision to the Act. *See, e.g., id.* at S11,836-37 (statement of Sen. Allard).

In the face of the long and unbroken history of failure-to-warn litigation over drug products, and Congress's refusal to add a preemption provision to federal law, this Court should be especially wary of taking a step that Congress has refrained from taking. There can be no question that Congress is well aware of the dynamic between state failure-to-warn litigation and FDA regulation of drug labeling. And there can be no question that Congress has decided that the two systems ought to co-exist, notwithstanding any tension that might arise, because the benefits of permitting the systems to operate in tandem outweigh any costs that might be incurred. That decision is plainly one that Congress is empowered to make.

This point takes on additional force here, because the "evidence" of the tension between FDA regulation of drugs and state failure-to-warn litigation is not simply thin, it is non-existent. Instead of coming forward with hard evidence of actual conflicts — that is, cases in which FDA's primacy over drug labeling has been compromised or even seriously threatened by

failure-to warn litigation — petitioner and the United States rely on what are at most predictive judgments that are unanchored in history. This Court's conflict preemption jurisprudence requires far more than that. *See, e.g., Sprietsma v. Mercury Marine*, 537 U.S. 51 (2002) (refusing to find conflict preemption where there was no evidence that application of state law would frustrate federal interests); *Geier v. American Honda Motor Co.*, 529 U.S. 861, 881-83 (2000) (finding conflict preemption based on an after-the-fact assessment of actual frustration of federal interests). For these reasons, the Court should affirm the judgment below.

CONCLUSION

For the reasons set forth above and in respondent's brief, the judgment below should be affirmed.

Respectfully submitted,

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August 14, 2008

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IN THE

Supreme Court of the United States

WYETH,

Petitioner,

v.

DIANA LEVINE,

Respondent.

On Writ of Certiorari to the Vermont Supreme Court

BRIEF OF THE GENERIC PHARMACEUTICAL ASSOCIATION AS *AMICUS CURIAE* IN SUPPORT OF PETITIONER

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June 3, 2008

WILSON-EPES PRINTING CO., INC. – (202) 789-0096 – WASHINGTON, D. C. 20002

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QUESTION PRESENTED

Whether federal drug labeling laws preempt state-law tort claims that seek to hold drug manufacturers liable for using FDA-approved labeling.

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STATEMENT OF INTEREST[1]

The Generic Pharmaceutical Association ("GPhA") is a non-profit, voluntary association comprised of more than 140 manufacturers and distributors in the generic pharmaceutical industry, which in turn accounts for more than 63 percent of prescriptions dispensed in the United States each year. GPhA's members provide American consumers with safe and cost-effective medicines that are bioequivalent to, and have the same therapeutic value as, their brand-name counterparts. These products significantly improve public health while cutting annual healthcare costs by billions of dollars.

GPhA's members have a strong interest in preserving the Food and Drug Administration's exclusive authority over drug product labeling, and in the national uniformity that FDA's labeling pre-approval process provides. That is so not only because lay juries are especially ill-suited to second-guess FDA's expert labeling decisions, *see Riegel v. Medtronic*, 128 S.Ct. 999, 1008 (2008), but because allowing lay juries to impose disparate, state-specific labeling mandates through tort litigation threatens to subject drug manufacturers—and generic drug manufacturers *in particular*—to directly conflicting

---

[1] All parties have consented to the filing of this brief, and letters evincing such consent have been filed with the Clerk. Pursuant to this Court's Rule 37.6, *amicus* states that no counsel for a party authored any part of this brief and that neither such counsel, nor any party, nor any person or entity other than *amicus*, its members, or its counsel made a monetary contribution intended to fund the preparation or submission of this brief.

state and federal requirements. Indeed, federal law expressly requires each generic drug product to bear "the same" labeling FDA approved for use on that product's brand-name equivalent, so if lay juries nonetheless may require generic manufacturers to depart from the FDA-approved labeling—as one thinly-reasoned decision cited by the Vermont Supreme Court so held, *see* Pet. App. 12a (citing *Bell v. Lollar*, 791 N.E.2d 849, 855 (Ind. Ct. App. 2003))—it would be impossible for generic drug companies to comply with both their state and federal obligations.

That result is untenable, and GPhA's members have an obvious interest in seeing this Court restore the integrity and uniformity of the federal drug-labeling regime. GPhA respectfully asks this Court to reverse the Vermont Supreme Court's judgment.

SUMMARY OF THE ARGUMENT

GPhA fully supports the arguments that Wyeth makes in support of reversing the Vermont Supreme Court's decision. But whatever the merits of that decision may be with respect to the labeling rights and responsibilities of brand-name manufacturers like Wyeth, the case for federal preemption is even stronger with respect to state-law tort claims that challenge the sufficiency of FDA-approved labeling for generic drug products.

That is so because federal law expressly requires each generic drug product to bear "the same" labeling that FDA approved for use on the generic drug product's brand-name equivalent. 21 U.S.C. § 355(j)(2)(A)(v). As a result, FDA consistently has made clear that the labeling regulation on which the Vermont Supreme Court based its decision, 21 C.F.R. § 314.70(c)(6)(iii) (the "CBE regulation"), does not

apply to generic drug products at all, and that generic drug manufacturers categorically may not deviate from the FDA-approved labeling. *See, e.g.*, Supplemental Applications Proposing Labeling Changes for Approved Drugs, Biologics, and Medical Devices, 73 Fed. Reg. 2848, 2849 n.1 (proposed Jan. 16, 2008) (to be codified at 21 C.F.R. § 314) ("CBE changes are not available for generic drugs approved under an abbreviated new drug application under 21 U.S.C. 355(j). To the contrary, a generic drug manufacturer is required to conform to the approved labeling for the listed drug.") (citations omitted).

With its sweeping declaration that FDA's labeling requirements merely "create a floor, not a ceiling, for state regulation," Pet. App. at 6, and unqualified assertion that "FDA approval of a drug label [is] but a first step in the process of warning consumers," *id.* at 15a, however, the Vermont Supreme Court's decision in this case threatens to subject generic drug manufacturers to directly conflicting state and federal requirements: either comply with federal law by replicating the label FDA's scientific experts approved for use on the generic drug's brand-name equivalent, and thereby risk potentially ruinous tort liability if a lay jury later takes issue with FDA's expert assessment of the label's sufficiency, or comply with the disparate labeling requirements imposed by lay juries in state-law tort litigation, and thereby risk potentially ruinous federal liability—including the withdrawal of FDA approval to market the drug, *see* 21 C.F.R. § 314.150(b)(10), and the imposition of sanctions for marketing a misbranded drug product. *See* 21 U.S.C. §§ 331, 333, 352.

That result cannot possibly be squared with the Supremacy Clause, and GPhA respectfully asks this Court to recognize that there is no lawful basis for allowing labeling-based state-law tort claims against generic drug manufacturers to proceed.

RELEVANT REGULATORY BACKGROUND

In order to promote the development, production, and marketing of affordable generic medicines, the Hatch-Waxman amendments to the Food, Drug, and Cosmetic Act ("Hatch-Waxman") establish an expedited FDA review process for proposed generic drugs and create significant incentives for generic manufacturers to enter the market. *See generally* 21 U.S.C. § 355(j) (2007); *see also Purepac Pharm. Co. v. Thompson*, 354 F.3d 877, 879 (D.C. Cir. 2004); *Mead Johnson Pharm. Group v. Bowen*, 838 F.2d 1332, 1333 (D.C. Cir. 1988).

To that end, Hatch-Waxman allows FDA to approve proposed generic drug products without requiring their manufacturers to conduct the same kind of extensive investigational studies and clinical trials that must be performed before most brand-name drugs can be approved. *Cf.* 21 U.S.C. § 355(b)(1)(A); 21 C.F.R. § 314.50(d). Instead, FDA may approve a proposed generic drug without such studies if the generic drug's manufacturer can prove that its product is bio- and therapeutically equivalent to a brand-name drug that FDA previously determined to be safe and effective. 21 U.S.C. § 355(j)(2)(A).

Because the whole premise of Hatch-Waxman's streamlined review process for proposed generic drugs is that such drugs are indistinguishable from their brand-name counterparts, the statute naturally

seeks to ensure that the labeling on every generic drug product is indistinguishable from the labeling FDA approved for that product's brand-name equivalent. Each application for a proposed generic drug (or "ANDA") therefore must include "specimens of the labeling proposed to be used for [the generic] drug," *id.* § 355(j)(2)(A)(vi) (cross-referencing 21 U.S.C. § 355(b)(1)(F)); proof that "the conditions of use prescribed, recommended, or suggested in the labeling proposed for the [generic] drug have been previously approved for a [brand-name] drug," *id.* § 355(j)(2)(A)(i); and, most important, proof "that the labeling proposed for the [generic] drug is *the same* as the labeling approved for the [brand-name] drug ... except for changes required ... because the [generic] drug and the [brand-name] drug are produced or distributed by different manufacturers." *Id.* § 355(j)(2)(A)(v) (emphasis added). To implement that mandate, FDA's regulations in turn require generic applicants to submit a "side-by-side comparison of the[ir] proposed labeling [and] the approved labeling for the [brand-name] drug with all differences annotated and explained." 21 C.F.R. § 314.94(a)(8)(iv).

Despite Hatch-Waxman's expedited review process, years sometimes pass between the date an ANDA first is submitted to FDA and the date FDA approves it. Special problems thus arise when changes are made to a brand-name drug's labeling after an ANDA applicant first seeks marketing approval for a generic version of that drug—including interim labeling changes that brand manufacturers may effectuate without FDA pre-approval in extraordinary circumstances. *See* 21 C.F.R. § 314.70(c)(6)(iii).

In such cases, FDA consistently has required generic applicants to replicate the latest *FDA-approved* version of the brand-name drug's label—and flatly prohibits them from replicating any *unapproved* labeling that the brand manufacturer implemented through the CBE process, or otherwise adding new warnings not contained in the brand-name product's approved labeling. *See, e.g.*, Abbreviated New Drug Application Regulations, 57 Fed. Reg. 17950, 17961 (Apr. 28, 1992); GPhA App. 13a-15a (Letter from Douglas L. Sporn, Director, Office of Generic Drugs, Center for Drug Evaluation and Research, to All ANDA and AADA Applicants (Dec. 24, 1996)); GPhA App. at 26a (Office of Generic Drugs, *Guidance For Industry: Revising ANDA Labeling Following Revision of the RLD Labeling* (May 2000)).

At the same time, FDA consistently has made clear that generic manufacturers, in marked contrast to their branded counterparts, are not entitled to use the CBE regulation to effectuate their own labeling changes without prior FDA approval. *See, e.g.*, Supplemental Applications Proposing Labeling Changes for Approved Drugs, Biologics, and Medical Devices, 73 Fed. Reg. 2848, 2849 n.1 (proposed Jan. 16, 2008) [the "CBE Interpretive Guidance"]; 57 Fed. Reg. 17950, 17953, 17961 (Apr. 28, 1992)); *see also* Br. of the United States as *Amicus Curiae*, *Colacicco v. Apotex, Inc.*, No. 05-CV-05500-MMB (E.D. Pa. filed May 10, 2006) [the "Colacicco Amicus Br."], at 6, *unpaginated full-text reproduction available at* 2006 WL 1724170.

Finally, federal law subjects generic companies to strict penalties for marketing drug products that

bear labeling which deviates from the labeling FDA approved for use on the brand-name equivalent. Hatch-Waxman itself prohibits FDA from approving an ANDA if "information submitted in the application is insufficient to show that the labeling proposed for the [generic] drug is the same as the labeling approved for the [brand-name] drug referred to in the application." 21 U.S.C. § 355(j)(4)(G). In turn, FDA's implementing regulations authorize the withdrawal of a generic drug's approval if its labeling "is no longer consistent with that for the [brand-name] drug referred to in the [ANDA]." 21 C.F.R. § 314.150(b)(10). And whether or not manufacturers can continue to market a drug product with inconsistent labeling, generic companies may be subjected to draconian penalties for having marketed a "misbranded" drug product to consumers. 21 U.S.C. § 331 (liability for misbranding); 21 U.S.C. § 333 (penalties for misbranding); 21 U.S.C. § 352 (definition of misbranding); *see also* Colacicco Amicus Br. at 15 & n.6, 17.

ARGUMENT

Federal Drug Labeling Laws Preempt State-Law Tort Claims That Seek To Hold Drug Manufacturers Liable For Using FDA-Approved Labeling.

The Vermont Supreme Court erred by holding that federal drug labeling laws permit state-law tort claims that seek to hold drug manufacturers liable for using FDA-approved labeling. Federal law preempts state laws (including state-law causes of action) that "make it 'impossible' for private parties to comply with both state and federal law," *Geier v. American Honda Motor Co.*, 529 U.S. 861, 873, 881

(2000), or which otherwise "stand[] as an obstacle to the accomplishment and execution of the full purposes and objectives of Congress." *Hines v. Davidowitz*, 312 U.S. 52, 67 (1941). Yet that is precisely what the Vermont Supreme Court's decision threatens to do. Plaintiffs are free to challenge FDA's prior labeling determinations or seek prospective product-labeling changes by lodging complaints directly with FDA, but federal law precludes them from doing so by bringing state-law tort claims in court.

The Vermont Supreme Court, however, asserted that federal law permits such claims to proceed because FDA's CBE regulation purportedly allows drug manufacturers to institute new labeling precautions "without prior FDA approval" and, thus, that "federal labeling requirements create a floor, not a ceiling, for state regulation." Pet. App. 6a; *see also id.* at 10a-11a ("[The CBE] regulation ... allows a drug's manufacturer to alter the drug's label without prior FDA approval when necessary.... While specific federal labeling requirements and state common-law duties might otherwise leave drug manufacturers with conflicting obligations, [the CBE regulation thus] allows manufacturers to avoid state failure-to-warn claims without violating federal law."); *id.* at 15a ("[The CBE regulation] does not allow us to interpret FDA approval of a drug label as anything but a first step in the process of warning consumers. When further warnings become necessary, the manufacturer is at least partially responsible for taking additional action, and if it fails to do so, it cannot rely on the FDA's continued approval of its labels as a shield against state tort liability."); *id.* at 23a ("Congress did not intend to

interfere with state prerogatives except where doing so is absolutely necessary, and the plain language of the [CBE] regulation makes such interference unnecessary here.") (internal cross-reference omitted).

As Wyeth well explains, those claims incorrectly characterize certain rights and responsibilities of brand manufacturers under the CBE regulation, and various aspects of FDA's role in regulating the labeling of brand-name drugs. *See, e.g.*, Wyeth Br. at 34-40. But whatever the merits of those claims may be with respect to the labeling of brand-name drug products, those claims are just plain wrong when it comes to the labeling rights and responsibilities of generic manufacturers and FDA's role in policing the labeling of generic drug products.

Federal law expressly mandates that the labeling on each generic drug product must be "the same" as the labeling FDA approved for use on the product's brand-name equivalent, 21 U.S.C. § 355(j)(2), and every other conceivable source of federal law either replicates or otherwise implements that plain statutory requirement. To that end, FDA's Hatch-Waxman regulations reiterate the statutory mandate and also require generic applicants to submit a side-by-side comparison of the brand-name and proposed generic labeling so that FDA can ensure that the respective product labels are substantively identical. 21 C.F.R. § 314.94(a)(8)(iv). Indeed, FDA flatly rejected a proposal at the time it adopted those regulations that would have allowed generic manufacturers "to deviate from the labeling for the [brand-name] drug to add contraindications, warnings, precautions, adverse reactions, and other

safety-related information," 57 Fed. Reg. at 17961—explaining both that Hatch-Waxman expressly requires each proposed generic drug "product's labeling [to] be the same as the [brand-name] drug product's labeling because the [brand-name] drug product is the basis for [generic drug product] approval," and that "[c]onsistent labeling will assure physicians, health professionals, and consumers that a generic drug is as safe and effective as its brand-name counterpart." *Id.*

Since that time, FDA repeatedly has warned generic applicants to conform their product labeling to the latest FDA-approved labeling for the brand-name equivalent—regardless of any interim, manufacturer-initiated changes to the brand-name product labeling. *See, e.g.*, GPhA App. 15a (warning that generic applicants should "NOT utilize the Physician's Desk Reference (PDR) as the source for the most recently approved labeling of the innovator's product," because "some of this labeling may have been ... implemented prior to FDA approval" and "*FDA must ... approve [such] labeling before it is acceptable for use as model labeling for an ANDA/AADA product*") (capitalization in original; emphasis added); *see also* GPhA App. 26a, 28a (explaining that "[t]he sponsor of an ANDA is ... responsible for ensuring that the labeling contained in its application is the same as the *currently approved* labeling of the [branded equivalent]," and instructing ANDA sponsors to "submit revised labeling" to FDA when "labeling changes [are] needed because of *approved changes* to the labeling of the [branded equivalent]") (emphasis added).

Perhaps most important, FDA long has made clear—and just recently reiterated—that generic drug manufacturers are not entitled to use the CBE regulation to effectuate unapproved product-labeling changes under any circumstances. *See, e.g.*, 73 Fed. Reg. at 2849 n.1 ("CBE changes are not available for generic drugs approved under an abbreviated new drug application under 21 U.S.C. 355(j). To the contrary, a generic drug manufacturer is required to conform to the approved labeling for the listed drug."); *see also* Colacicco Amicus Br. at 6 ("For a generic drug manufacturer, there is no statutory or regulatory provision permitting the manufacturer to make a labeling change to its generic drug without prior FDA approval. To the contrary, a generic drug manufacturer is required to conform to the approved labeling for the listed drug."); *id.* at 17 ("[A] generic drug manufacturer is not permitted to add a warning or caution to the label without prior approval from FDA.") (citing 21 U.S.C. §§ 355(j)(2)(A)-(C); 21 C.F.R. § 314.150(b)(10)).

Regardless of whether the CBE regulation permits brand manufacturers to effectuate labeling changes without prior FDA approval, and without respect to the particular conditions under which they may (or may not) do so, it thus is beyond serious dispute that federal law flatly prohibits generic drug manufacturers from initiating their own labeling changes; adding new warnings without first securing FDA pre-authorization; or otherwise deviating from the latest labeling that FDA has approved for a given generic drug product's brand-name equivalent.

As a result, there is no conceivable basis for applying the Vermont Supreme Court's decision—

which hinged entirely on the conclusion that FDA's CBE regulation authorizes manufacturers to initiate labeling changes without FDA pre-approval, *see, e.g.*, Pet. App. 10a-11a, 15a, 23a—in cases involving state-law claims against generic manufacturers, for whom the CBE process is unavailable. Indeed, applying the state court's decision in such cases would subject generic companies to directly conflicting state and federal labeling requirements in clear violation of the Supremacy Clause.

If, on one hand, generic companies heed federal law by maintaining their FDA-approved labeling, they would risk significant monetary damages in state-law tort litigation that seeks to second-guess FDA's expert labeling determinations. *See* Pet. App. 12a (citing *Bell*, 791 N.E.2d at 855 (holding that generic manufacturers are subject to state-law tort liability despite Hatch-Waxman's explicit requirement that they use only FDA-approved labeling)). And if, on the other hand, generic manufacturers yield to the pressure of state-law tort litigation by modifying their labeling to meet state-law requirements, there is no question that they would face significant federal sanctions—including the revocation of FDA marketing approval, 21 C.F.R. § 314.150(b)(10), and (as FDA recently reiterated) the imposition of potentially draconian sanctions for marketing a misbranded product. *See, e.g.*, 21 U.S.C. §§ 331, 333, 352; Colacicco Amicus Br. at 15 & n.6, 17; *see also Colacicco v. Apotex, Inc.*, 432 F. Supp. 2d 514, 537-38 (E.D. Pa. 2006) (rejecting claims that generic manufacturers can be subjected to state-law labeling suits due to conflict with federal law); *Conte v. Wyeth, Inc.*, No. CGC-04-437382, 2006 WL 2692469 (Cal. Super. Ct. Sept. 14, 2006) (same).

It goes without saying that the Supremacy Clause is designed precisely to prevent regulated parties from being forced to make such intolerable choices, and thus requires state interests to give way whenever their pursuit would conflict with federal mandates. *See, e.g., Gade v. National Solid Wastes Mgmt. Ass'n*, 505 U.S. 88, 108 (1992) ("[U]nder the Supremacy Clause, from which our pre-emption doctrine is derived, 'any state law, however clearly within a State's acknowledged power, which interferes with or is contrary to federal law, must yield.'") (quoting *Felder v. Casey*, 487 U.S. 131, 138 (1988)); *Florida Lime & Avocado Growers, Inc. v. Paul*, 373 U.S. 132, 143 (1963) ("[F]ederal exclusion of state law is inescapable ... where compliance with both federal and state regulations is a physical impossibility.").

That is precisely the case here, and GPhA thus respectfully asks this Court to overturn the Vermont Supreme Court's decision or otherwise make clear that the lower court's reasoning cannot be applied to state-law claims challenging the sufficiency of generic drug labeling.

CONCLUSION

For the foregoing reasons, the Vermont's Supreme Court's judgment should be reversed.

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DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Rockville, MD 20857

DEC 24, 1996

TO ALL ANDA AND AADA APPLICANTS

Dear Sir or Madam:

As part of the ongoing initiatives to reinvent government, the Office of Generic Drugs (OGD), like most other Federal programs, is faced with reduced resources. In addition to diminishing resources, OGD experienced a significant increase in submissions in late 1995. This higher level of submissions has continued in 1996. These combined factors resulted in an increased backlog of pending submissions. In order to help minimize the impact of these factors on review times, OGD began a series of internal meetings to identify procedures that would help streamline the review process. In addition, OGD believes these efforts will improve communications with industry and reduce the overall time to approval of abbreviated applications.

This letter describes the first streamlining initiatives that affect the chemistry, bioequivalence and labeling review processes. OGD looks forward to implementing additional streamlining initiatives in the future. The letter also contains an update on a variety of application related matters that will be of interest to applicants.

The Office trusts the information will be useful to you. Your cooperation in these matters will assist us

in our effort to improve the efficiency of the generic drug review process.

Sincerely yours.

/s

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation
and Research

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REVIEW ISSUES

COMMUNICATING NOT APPROVABLE DETERMINATIONS

Effective January 1, 1997, the Office of Generic Drugs (OGD) will provide most application related "not approvable" deficiencies, both major and minor, to ANDA/AADA holders via facsimile for unapproved original applications. This is expected to decrease time to final action on applications. However, for the present time, the Division of Bioequivalence will continue to issue deficiency letters as it has always done.

The facsimile will include the usual components of a deficiency letter, but not in the traditional letter format. It will include:

A. A list of chemistry, manufacturing, and controls (CMC) deficiencies followed by additional CMC comments regarding status of methods validation, pre-approval inspection, and other related points.

B. A list of labeling deficiencies.

C. A list of microbiology deficiencies, if applicable.

A cover sheet will accompany the deficiency list which will provide instructions on how to respond to the facsimile.

To assist the Office in providing the facsimiles, applicants are requested to provide or update the facsimile number for its Regulatory Affairs contact person.

MAJOR NOT APPROVABLE DEFICIENCY PROCEDURES

Major CMC deficiencies identified by OGD will be sent to the applicant by facsimile. Responses from

the applicant to these deficiencies will be regarded as a major amendment and should be submitted as an archival (hard) copy to OGD. OGD will not accept facsimile responses for major deficiencies.

MINOR NOT APPROVABLE DEFICIENCY PROCEDURES

For CMC deficiencies defined as minor, OGD will also communicate to the applicant by facsimile. The facsimile cover sheet that OGD sends to an applicant will identify the deficiency response as either a "Facsimile Amendment" or a "Minor Amendment". Procedures for responding to these two types of amendments are as follows:

A. Facsimile Amendment

There will be some minor deficiencies for which OGD believes a complete response can be provided by the applicant within 30 days. These deficiencies will be provided by facsimile and will NOT stop the regulatory review clock.

The applicant will be asked to respond directly to OGD's document room by facsimile, followed with a hard copy. Facsimile amendments will be reviewed ahead of other priority of routine submissions pending in the reviewer's queue.

Should the complete response (facsimile and hard copy) not be received within 30 days, the applicant's response will be considered a minor amendment and placed into the reviewer's minor amendment queue.

B. Minor Amendment

There will be some minor amendments for which a response cannot be provided within

30 days. These will typically be for situations when the response is beyond the control of the applicant, *e.g.*, Drug Master File (DMF) deficiencies. OGD will provide these deficiencies by facsimile and will STOP the regulatory review clock. In addition, the applicant's response (minor amendment) should be submitted as an archival (hard) copy to OGD and will be placed into the reviewer's queue according to OGD's first-in, first-reviewed policy. OGD will not accept facsimile responses for these minor amendments.

In order to evaluate the expected benefits of this new process, the Office will be monitoring the impact on action times. However, reports of industry experiences with this process are encouraged.

PHONE CONSULTATION FOLLOWING SECOND REVIEW CYCLE WITH MAJOR DEFICIENCIES

Applicants who find that an application continues to have major CMC deficiencies after the second review cycle are encouraged to call the appropriate Project Manager (PM) in OGD to discuss or clarify the deficiencies. Where appropriate the PM will involve the chemistry reviewer and/or others in the discussion. The goal is to answer questions, assist the applicant to understand the identified deficiencies and, hopefully, eliminate further major deficiency reviews. In some cases meetings may be necessary to clarify these deficiencies. OGD will contact the applicant within approximately 30 days after issuance of the second major deficiency letter if the Office has not been contacted by the applicant. OGD will also use the same approach for subsequent reviews where major deficiencies remain.

Currently, OGD is unable to provide this level of service after the first review cycle due to the volume of such submissions and the Office's limited resources.

ALTERNATE DRUG SUBSTANCE FOR ORIGINAL APPLICATIONS

The Office of Generic Drugs has announced a change in policy regarding adding an alternate source of the new drug substance (NDS) to an original application prior to approval.

Previously, if an abbreviated application was otherwise approvable with the exception of an unsatisfactory inspection of current Good Manufacturing Practices (cGMP) for the primary NDS supplier used to manufacture the exhibit/bioequivalence batch, it would not be approved until those cGMP issues were resolved. In order to qualify an acceptable alternate source of the NDS, a new exhibit batch based on the alternate source would be needed. Additionally, a bioequivalence study would be required (depending on dosage form) to support use of the alternate source.

For unapproved applications, OGD now allows substitution of an alternate source of the new drug substance based on assurance that the specifications and test data are essentially the same as those of the original source used in the exhibit batch (and bioequivalence study, if required) that would have been acceptable except for cGMP issues, etc. Additionally, the DMF must be found acceptable. Generally, a new *in vivo* bioequivalence study will not be required for the alternative dissolution data depending on the dosage form of the proposed product. This new policy is identical to the existing

policy regarding post approval changes to provide for alternate sources of the NDS.

Note that there are some situations where this new policy would not apply and a new acceptable exhibit batch, and *in vivo* bioequivalence study, and comparative dissolution data would be required. This might be the case when there are significant differences in particle size of physicochemical characteristics.

BIOEQUIVALENCE ISSUES

ELECTRONIC SUBMISSION PROJECT

Effective January 1, 1997, the Office of Generic Drugs will implement its program for electronic submission of bioequivalence data. The program was developed under contract with the University of Maryland (UM). Under the program, applicants that choose to, may prepare electronic submissions on diskette with the aid of a user-friendly program call Entry and Validation Program (EVA). EVA is free of charge to applicants through the UM's World Wide Web site (http://mundos.ifsm.umbc.edu/-fdacom). The Web site also permits applicants to register as participants and to obtain updated information on he program including any new versions of EVA. Companies can also ask technical questions through the Web site, which will be addressed by UM staff.

The program is expected to have a very positive impact on the efficiency of reviews, ultimately reducing review times. In addition, it is hoped the program will help reduce the time required to reach approval. Therefore, OGD strongly encourages firms to participate.

For most companies, the time to start planning the electronic submission is before study data are

prepared. For those using Contract Research Organizations (CROs) to conduct bioequivalence studies, applicants could specify in their requirements that the CROs prepare the data in the requested format. CROs are encouraged to access the UM Web site and to become familiar with EVA and submission requirements. Applicants may also make electronic submissions for applications already submitted to the office, but should contact the Bioequivalence Project Manager (Ms. Lizzie Sanchez, 301-594-2290) first, to make certain the electronic submission will be received in time for the review.

We hope to conduct training for applicants in conjunction with UM. Those applicants interested in such training are encouraged to register their interest through the UM Web site. Technical questions about the program may be addressed to the UM at 410-455-3888 or through the UM Web site. Regulatory questions may be addressed to the Bioequivalence Project Manager.

The electronic submission program is part of a larger strategy for Electronic Regulatory Submission and Review (ERSR) which will soon include the chemistry, manufacturing, an controls (CMC) portion of generic drug applications.

AVAILABILITY OF BIOEQUIVALENCE PROTOCOL REVIEWS

Firms frequently submit proposed *in vivo* bioequivalence study protocols to OGD. Often these are duplicative of already submitted and reviewed protocols. In order to decrease the burden of reviewing several protocols for the same drug product, OGD is now making available copies of acceptable protocols and related review comments. OGD believes that by utilizing completed review

comments, firms will need to submit fewer protocols, freeing time for evaluation of applications. Copies may be obtained from the Drug Information Branch, HFD-210, Center for Drug Evaluation and Research, 5600 Fishers Lane, Rockville, MD, 20857. The current phone number for the Drug Information Branch is (301) 827-4573. Please note that this number was recently changed because that branch relocated.

The list of protocols available may be accessed through "FAX on Demand" at (800) 342-2722 or (301) 827-0577. You are encouraged to obtain an updated list by this means. However, the Division of Bioequivalence will also maintain a listing.

There are caveats to be borne in mind regarding this new resource:

A. The material available will be redacted protocols and letters transmitting the review comments.

B. It will take some time to prepare protocols and reviews for distribution through this process. Therefore, the number of different product protocols and review will gradually increase, over time.

C. The procedure is new and may require fine tuning. Thus, comments and suggestions are encouraged. These may be submitted to Ms. Lizzie Sanchez at (301) 594-2290.

D. There will be a transition period during which firms with pending requests for protocol review may be contacted regarding the imminent availability of a review of another protocol regarding the product for which they had submitted a protocol. The firm may wish

to withdraw its protocol and use information available from the previously acceptable review.

Please note that though this service is available, the Division may be contacted should there appear to be circumstances necessitating review of another protocol for the same drug product.

UPDATE ON ALBUTEROL INHALATION AEROSOL GUIDANCE

On January 27, 1994, OGD issued the guidance titled "Interim Guidance for Documentation of *in vivo* Bioequivalence of Albuterol Inhalation Aerosols (Metered Dose Inhalers)." Since its publication, the Office has had the opportunity to review additional information on various aspects of *in vivo* and *in vitro* testing conducted as described in the guidance and has concluded that a revision of the guidance is needed. A CDER working group developed recommendations for revision and presented them to a joint session of the Advisory Committee for Pharmaceutical Science (ACPS) (a re-configuration of the Generic Drug Advisory Committee — GDAC) and the Pulmonary Drugs Advisory Committee in August of 1996.

Therefore, should studies for albuterol metered dose inhalers (MDIs) be under consideration, sponsors are strongly encouraged to wait for the revised-guidance, or, in the interim, discuss their planned study with the Division of Bioequivalence. The guidance will be developed as expeditiously as possible and the industry will be informed of its availability.

BIOEQUIVALENCE STUDIES TO BE CONDUCTED IN APPROPRIATE SUBJECTS

Though it is preferable to conduct bioequivalence testing in normal healthy volunteers, there are

certain products for which use in healthy persons might be an unacceptable risk.

A. Cytotoxic drugs

Certain conditions and considerations regarding bioequivalence studies of cytotoxic drugs need to be specified. Please note the following:

21 CFR 320.31(a)(3) requires that any person planning to conduct an in vivo bioavailability or bioequivalence study in humans shall submit an investigational new drug application (IND). An IND provides assurance that studies proposed will have adequate safeguards for the safety of the subjects.

It is therefore recommended that studies with the following products be conducted in the appropriate patient population. Note also that the listing (developed in conjunction with the Division of Oncologic Drug Products) is subject to the updating and revision. Consultation with the Office is recommended if any questions arise.

Bisulfan	Chlorambucil
Cyclophosphamide	Etoposide
Hexamethylmelamine	Lomustine
Melphalan	Pipobroman
Procarbazine	Thioguanine
Uracil Mustard	Methoxsalen
Estramustine Phosphate	

B. Ipratroprium

In order to fully evaluate the bioequivalence of this product, studies should be conducted in the appropriate patient population.

IN VIVO STUDIES UNDER SUPAC-IR

Under the Center's Guidance for Industry: Immediate Release Solid Oral Dosage Forms (SUPAC-IR) there are two types of post-approval changes for which *in vivo* bioequivalence testing is requested: Level 3 changes in components and composition as well as Level 3 manufacturing process changes. For generic drugs, the *in vivo* bioequivalence test should always compare the product after a post-approval change against the reference listed drug. However, in instances when a bioequivalence study is not necessary, dissolution studies should compare the applicant's generic product after a post-approval change against the same product prior to the change.

If there are any questions in regard to a reference product, please contact the Division of Bioequivalence for advice.

LABELING REVIEW CHANGES

The abbreviated application regulations require that side-by-side labeling comparisons be included with the submission of the original, unapproved application, with all differences between the proposed ANDA/AADA and the reference listed drug (RLD) labeling annotated and fully explained [See 21 CFR 314.94(a)(8)]. Side-by-side comparisons enable reviewers to readily identify differences between the ANDA/AADA and the reference listed drug labeling and/or the previous version of the applicant's labels and labeling.

OGD is now requesting a side-by-side comparison for all labeling changes submitted, not only in original applications, but also for all amendments and supplements. This comparison will help reduce

the time required to review each new version of proposed labeling.

Additional actions to streamline the labeling review process have resulted in the following changes:

A. OGD will provide pen and ink comments directly on a applicant's proposed labeling and attach those comments to the Not Approvable facsimile. This will eliminate the time consuming task of identifying where in the labeling changes should be made and explaining the needed changes in letter format. This will conserve reviewer's time, thus making more efficient use of OGD resources.

B. Effective immediately, when changes are needed in labeling because of changes in the RLD labeling, OGD will either identify the specific changes to be made or will provide a copy of the most recently approved labeling of the RLD. In the past when MAJOR changes were required in the labeling, the applicant was required to obtain a copy of the cited approved labeling from the Freedom of Information (FOI) staff, then submit a supplement or amendment. This process added 4 to 6 weeks to the process of updating the ANDA/AADA labeling.

   Please note that OGD will NOT supply labeling of the RLD BEFORE an application is filed. The most recent APPROVED labeling should be obtained from the FOI staff prior to preparation and submission of the labeling in an ANDA/AADA.

The Division of Labeling and Program Support highly recommends that ANDA/AADA applicants NOT utilize the Physician's Desk Reference (PDR) as the source for the most recently approved labeling of the innovator's product. Although the PDR may represent labeling that is available in the marketplace, some of this labeling may have been submitted to the Agency as a "Special Supplement - Changes Being Effected" (SSCBE). As such, it would have been implemented prior to FDA approval in accordance with 21 CFR 314.70(c). The FDA must still review, possibly recommend changes and approve the labeling before it is acceptable for use as model labeling for an ANDA/AADA product. In addition, other changes may have been made in the approved labeling after the publication of the PDR.

APPLICATION PROCESS ISSUES

Refusal to File Issues

The Office evaluates abbreviated applications for completeness and acceptability prior to filing them for review. OGD has identified many issues which previously would have resulted in refuse [sic] to file determinations which can be easily resolved by applicants. These are now communicated by OGD by telephone rather than issuing a letter which can take weeks. Such items include:

No cGMP statement
FDA Form 356h does not contain an original signature
Improper patent certification
Exclusivity rights not addressed
No debarment/list of convictions statement
No certification of field copy
Need for additional copies of labeling

Applicants are given 10 working days to respond. If a response is not received in that time, a refuse to file letter is issued.

This approach has resulted in a decrease in refuse to file determinations and moves applications into the review queue more rapidly. Even with this approach, the refuse to file rate for applications remains high. Therefore, an update of the key reasons the Office refuses to file abbreviated applications follows:

A. DMF Issues

No authorization for the Drug Master File (DMF) or incomplete information about the DMF.

The DMF authorization must be from the DMF holder or its U.S. agent to permit the agency to refer to the DMF on behalf of the applicant. If the authorization is from the agent, an additional letter of appointment of the agent must also be included from the holder of the DMF (link to DMF holder). The authorization for the agency to refer to the DMF must reference the specific applicant, not another corporate entity related to the applicant.

For further information please refer to the CDER Guideline for Drug Master Files.

B. Inactive Ingredient Issues

Inadequate information on the characterization of inactive ingredients.

The regulations related to parenteral, ophthalmic, otic and topical dosage forms [21

CFR 314.94(a)(9)] state that applicants shall identify and characterize the inactive ingredients in the proposed drug product and provide information demonstrating that the inactive ingredients do not affect the safety of the proposed drug product. Additionally, OGD's Interim Inactive Ingredients Policy dated November 17, 1994, address inactive ingredient issues in more detail. The Interim Inactive Ingredient Policy is available in the OGD Docket (No. 9050308).

Thus, applicants should demonstrate that the proposed drug product is qualitatively and quantitatively the same as the reference listed drug product for parenteral, ophthalmic, otic, and topical dosage forms. An applicant may seek approval of a drug product that differs from the RLD, in certain instances, as described in the regulations.

Generally, products for oral inhalation are considered topical products. Therefore, applicants for these products are requested to provide a qualitative and quantitative comparison. Please refer to the Interim Inactive Ingredient Policy for further guidance.

For other topical products, i.e., creams, lotions, gels, suspensions, and solutions an applicant is requested to provide the following information:

1. Qualitative Statement

   A list of ingredients (test drug and reference drug) to show a qualitative comparison.

2. Quantitative Statement

The quantitative composition of the test drug and the results of analysis of the reference drug. It may not be possible to accurately analyze some inactive ingredients contained in the reference product. However, applicants should make their best efforts to quantitatively analyze the ingredients in the reference drug and submit the results in the application. If an ingredient cannot be analyzed, or if results are irrelevant or inconclusive, an explanation should be provided. Sponsors may use the Center for Drug Evaluation and Research Inactive Ingredient Guide (IIG) as a reference for safe maximum levels. If the ingredient levels are not listed, the sponsor may also refer to other sources of information, such as other approved topical products where quantitative levels are known, recognized literature references or information from the ingredient manufacturer.

OGD does not require a quantitative or qualitative analysis beyond the normal analytical capabilities within the industry.

If applicants have questions regarding inactive ingredients, they may submit a request for the opinion of the OGD on the acceptability of inactive ingredients prior to the submission of an application. The Office can provide certain information in response to such requests.

C. Exclusivity Issues

Exclusivity right(s) or patent(s) not addressed.

Patents and exclusivity must be addressed. When there is no exclusivity or patent listed in the Orange Book, the applicant should provide a statement to this effect. It is also suggested that applicants verify they are using a current edition of the Orange Book and/or cumulative supplement as the basis for this information.

D. Packaging Information

No record of or incomplete packaging information on the exhibit batch.

This packaging information is requested in order for the application to be filed. This request is outlined in OGD's Policy and Procedure Guide #41-93.

ACCEPTANCE OF ANDA BASED ON A PENDING PETITION FOR A DETERMINATION OF REASONS FOR VOLUNTARY WITHDRAWAL OF THE REFERENCE LISTED DRUG

OGD can accept an Abbreviated New Drug Application that refers to a listed drug that has been voluntarily withdrawn from sales as long as the applicant provides evidence that a Citizen's Petition has been submitted to request a determination of whether a listed drug has been voluntarily withdrawn for safety or efficacy reasons. A Center response to that petition is not required for filing purposes. However, the Center must have made its determination on relisting prior to the approval of the ANDA. (See 21 CFR 314.161 and 314.122)

DOCUMENTATION OF APPROPRIATE AUTHORIZATION OF AGENTS

If is acknowledged that there are many circumstances that require applicants to have other parties interact with the OGD on their behalf relative to specific applications. Frequently, written authorization for these agents is not contained in an application when submitted. The Office wishes to be cooperative in its response to applicant needs but must assure submitted material remains confidential and is not released or discussed with unauthorized individuals.

In order to allow for prompt responses, it is requested that written authorization be submitted to the application when filed or well before contact by an authorized agent is expected. Examples of who requires such authorization include:

A. The U.S. agent of a foreign firm.

B. A consultant to the firm that is expected to interact directly with OGD.

C. Legal counsel to the firm on issues that may necessitate direct interaction with OGD.

INFORMATION FOR INSPECTIONS

United States agents for foreign establishments are very helpful to the Office of Compliance in assigning foreign inspections. It is, therefore, important that complete information (name, address, phone/fax numbers) of the U.S. agent be included in an application.

Central File Numbers (CFN) as identifiers for facilities are also of value in the scheduling of inspections. Please provide these numbers for all facilities included in the application. CFN's are

obtained by applying for them through the FDA District Offices.

OTHER

WITHDRAWAL OF APPLICATION

The Office requests that firms make periodic internal assessments and withdraw pending applications they may not wish to pursue to approval. This action will allow conservation of OGD's information tracking and document control resources.

Guidance for Industry

Revising ANDA Labeling Following Revision of the RLD Labeling

U.S. Department of Health and Human Services Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

May 2000
OGD

Guidance for Industry Revising ANDA Labeling Following Revision of the RLD Labeling

Additional copies are available from:

Office of Training and Communications
Division of Communications Management
Drug Information Branch, HFD-210
5600 Fishers Lane
Rockville, MD 20857
(Tel) 301-827-4573

(Internet)
http://www.fda.gov/cder/guidance/index.htm

U.S. Department of Health and Human Services Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

May 2000
OGD

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Guidance for Industry[1]

Revising ANDA Labeling Following Revision of the RLD Labeling

I. INTRODUCTION

This guidance is intended to assist sponsors of abbreviated new drug applications (ANDAs) in deciding when and how to submit labeling supplements following labeling revisions to their reference listed drugs (RLDs).

II. BACKGROUND

During the marketing life of a drug product approved under a new drug application (NDA), the package insert labeling is frequently revised. When an NDA serves as an RLD for an ANDA, approved changes in the RLD labeling generally necessitate changes in the labeling of one or more ANDAs using the RLD. Under the Federal Food, Drug, and Cosmetic Act and Agency regulations, an ANDA product must have the same labeling as the RLD.

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[1] This guidance has been prepared by the Office of Generic Drugs in the Office of Pharmaceutical Science, Center for Drug Evaluation and Research (CDER), at the Food and Drug Administration. This guidance document represents the Agency's current thinking on changes in labeling of approved abbreviated new drug applications (ANDAs) following revisions in the RLD's labeling. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes, regulation, or both.

Section 505(j)(2)(A)(v) of the Act states that an abbreviated application for a new drug must contain

> information to show that the labeling proposed for the new drug is the same as the labeling approved for the listed drug ... except for changes required because of differences approved under a petition ... or because the new drug and the listed drug are produced or distributed by different manufacturers.

Similar statements are also found in the regulations at 21 CFR 314.94(a)(8)(iv).

Previously, OGD notified the appropriate ANDA sponsors when the approved labeling of their RLD changed. This was usually done using a formal supplement request letter. In cases where an NDA served as the RLD for multiple generic products, the preparation of a large number of request letters took a significant amount of review staff time. With the increase in the numbers of approved NDAs and ANDAs, this approach was using an increasingly disproportionate share of OGD's resources. Because of the time it took, the approach sometimes even delayed the notification of ANDA sponsors. With the exception of a few special situations (noted below), ***OGD is no longer providing this type of notification***. The sponsor of an ANDA is now responsible for ensuring that the labeling contained in its application is *the same as* the currently approved labeling of the RLD. OGD has determined that this change in responsibility is necessary to minimize the implementation time for the introduction of revised labeling into the market place. OGD believes that prompt revision, submission to the Agency, and

implementation of revised labeling are important to ensure the continued safe and effective use of generic drug products. Because the regulations state that the labeling of the generic must be the same as the innovator, the revision should be made at the very earliest time possible. If there is any potential delay in the revision of a generic drug labeling, the sponsor should contact OGD.

III. HOW TO OBTAIN INFORMATION ON A CHANGE IN RLD LABELING

The sponsor of an ANDA should routinely monitor the Labeling Review Branch Homepage (see below) for information on changes in labeling. OGD's Labeling Review Branch will:

- Place monthly updates of approved labeling changes for RLDs with approved ANDAs on the Labeling Review Branch Homepage at:

http://www.fda.gov/cder/ogd/rld/labelingreviewbranch.html

Continue to notify ANDA applicants by facsimile, telephone, and/or letter for any labeling revision approved for the RLD that warrants ***immediate*** widespread professional notification, such as those changes connected to issuing a *Dear Doctor Letter* or similar significant changes.

All approved labeling for RLDs is still available from Freedom of Information Staff. Sponsors who wish to obtain labeling using this mechanism should send a written or facsimile request to:

Food and Drug Administration
Freedom of Information Staff (HFI-35)
5600 Fishers Lane
Rockville, MD 20857
Phone: 301-827-6500; FAX: 301-443-1726

When a labeling revision is needed, the ANDA sponsor should take appropriate action to revise the ANDA labeling and submit the revised labeling to the FDA.

IV. HOW TO SUBMIT REVISED LABELING

All ANDA labeling changes needed because of approved changes to the labeling of the RLD may be submitted as a *Special Supplement - Changes Being Effected.* Such supplements should include:

- 12 copies of final printed labeling
- the date the revised labeling will be used (go into effect)
- a side-by-side comparison of the ANDA labeling with the approved labeling of the RLD with all differences annotated and explained, as described in 21 CFR 314.94(a)(8)(iv)

Sponsors should contact the OGD Labeling Review Branch at 301-827-5846 if there are any questions about the information in this guidance.

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No. 06-1249

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IN THE

Supreme Court of the United States

WYETH,

Petitioner,

v.

DIANA LEVINE,

Respondent.

ON WRIT OF CERTIORARI
TO THE SUPREME COURT OF VERMONT

BRIEF OF *AMICI CURIAE* MEMBERS OF CONGRESS IN SUPPORT OF RESPONDENT

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August 2008

BATEMAN & SLADE, INC. BOSTON, MASSACHUSETTS

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BRIEF OF *AMICI CURIAE* MEMBERS OF CONGRESS IN SUPPORT OF RESPONDENT

INTEREST OF *AMICI CURIAE*

The question presented in this case is whether to discard the well-settled understanding of Congress, courts around the country, and (until quite recently) the federal Food and Drug Administration ("FDA") that the Food, Drug, and Cosmetic Act of 1938 ("FDCA"), 21 U.S.C. § 301, *et seq.* does not preempt state-law failure-to-warn claims.

This brief is submitted on behalf of Senators Patrick J. Leahy, Edward M. Kennedy, Sheldon Whitehouse, Tom Harkin, Dianne Feinstein, Richard J. Durbin, Bernard Sanders, Russell D. Feingold, Representatives Henry A. Waxman, John Conyers, Jr., John D. Dingell, Frank Pallone, Jr., Bart Stupak, Zoe Lofgren, Linda Sánchez, Debbie Wasserman Schultz, Maxine Waters, and Peter Welch.

Amici curiae are Members of Congress with an important interest in this issue.[1] *Amici* include the Chairmen of the United States Senate and House Committees on the Judiciary, the Chairman of the Senate Committee on Health, Education Labor, and Pensions, the Chairman of the House Committee on Energy and Commerce, the Chairmen of the Subcommittee on Health and the Subcommittee on Oversight and Investigations of the House Committee

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[1] This brief has been filed with the written consent of the parties, which is on file with the Clerk of Court. No counsel for a party authored this brief in whole or in part, nor did any person or entity, other than *amici* or their counsel, make a monetary contribution to the preparation or submission of this brief.

on Energy and Commerce, and the Chairman of the House Committee on Oversight and Government Reform, as well as Members of these Committees. *Amici* have extensive experience in federal pharmaceutical regulation and federal preemption issues under the FDCA. *Amici* have participated in numerous legislative proceedings concerning FDCA preemption, most recently in the context of the Food & Drug Administration Amendments Act of 2007 ("FDAAA"), Pub. L. No. 110-85, 121 Stat. 823 (2007). *Amici* have conducted public hearings on the preemption issue, such as *Regulatory Preemption: Are Federal Agencies Usurping Congressional and State Authority?* Hearing Before the Senate Committee on the Judiciary, 110th Cong. 1st Sess. (Sept. 12, 2007) (hereafter "*Senate Regulatory Preemption Hearing*"), and *Should FDA Drug and Medical Device Regulation Bar State Liability Claims?* Hearing Before the House Committee on Oversight and Government Reform, 110th Cong. 2d Sess. (May 14, 2008) (hereafter "*House FDA Preemption Hearing*").

At bottom, this case presents a question of congressional intent. This Court has explained that "[t]he purpose of Congress is the ultimate touchstone in every pre-emption case." *Medtronic, Inc. v. Lohr*, 518 U.S. 470, 485 (1996) (citation and internal quotation marks omitted); *see also Cipollone v. Liggett Group, Inc.*, 505 U.S. 504, 516 (1992) (same). *Amici* are uniquely situated to address the question of congressional intent at the center of this case. Although *amici* submit this brief in their individual capacities, not on behalf of Congress itself, their views are informed by their experiences as Members of Congress.

SUMMARY OF ARGUMENT

At its core, "[p]re-emption fundamentally is a question of congressional intent." *English v. General Elec. Co.*, 496 U.S. 72, 78 (1990). Petitioner Wyeth ascribes to Congress a considered judgment to displace state tort remedies and strip consumers of their right to receive compensation for injuries caused by inadequate warnings on the part of drug manufacturers. But Congress has made no such judgment.

To the contrary: when Congress enacted the FDCA 70 years ago, it deliberately preserved state-law damages claims. Since that time, Congress has consistently understood that federal law does not preempt state-law failure-to-warn claims with respect to drugs approved by the FDA. This understanding has been fortified by settled practice under the statute. For decades, innumerable state-law actions involving FDA-approved pharmaceuticals have been prosecuted to final judgment or settlement. The courts and (until recently) the FDA have shared Congress' view that federal labeling rules create only minimum requirements and do not immunize drug companies from liability under state law. The widespread practice of permitting state-law claims, coupled with a common understanding of the statute's meaning among the courts, Congress, and the FDA, has created precisely the kind of "well-embedded [statutory] interpretation" that this Court has held is entitled to respect. *CBOCS West, Inc. v. Humphries*, 128 S.Ct. 1951, 1958 (2008).

In this case, the FDA has advanced a radical new legal position regarding the preemptive effect of the FDCA that represents a sharp break from the

practice of the past 70 years. The FDA now asserts that the Act displaces state failure-to-warn claims for federally approved drugs. This revolutionary change would bar the kind of traditional state-law actions that have been brought for decades under the FDCA.

Moreover, the agency's changed view represents a usurpation of authority properly belonging to Congress, the States, and the courts. The FDA would arrogate to itself the power to decide the preemptive force of the federal statute, which is a matter of congressional (and not administrative) intent. Whatever the FDA's view of its labeling regulation, *Congress* never intended to allow the FDA to adopt regulations that would preempt failure-to-warn lawsuits under state law. It is *congressional* intent, not FDA intent, that governs the preemption inquiry.

An agency cannot supplant Congress. As Justice Scalia has noted, "[a]gencies may play the sorcerer's apprentice but not the sorcerer himself." *Alexander v. Sandoval*, 532 U.S. 275, 291 (2001). The FDA's attempt to expand the preemptive scope of the regulatory scheme is nothing short of an illegitimate power grab. The FDA's position poses a threat not merely to injured consumers and the States, but also to the separation of powers and the constitutionally assigned role of Congress in our system of government.

Altering the construction of the FDCA at this late date would also frustrate congressional intent and impair the statutory system of federal prescription drug regulation. Far from standing "as an obstacle to the accomplishment and execution of the full purposes and objectives of Congress," state-law claims against pharmaceutical manufacturers

"necessarily perform an important remedial role in compensating" injured individuals and in encouraging drug safety. *Sprietsma v. Mercury Marine,* 537 U.S. 51, 64 (2002) (internal citations omitted). State tort law complements federal drug regulation by not only compensating those injured by misconduct but also by deterring future harm.

There are important reasons for holding that FDA approval of a drug label does not preempt state-law failure-to-warn claims. Manufacturers should be given the incentive to supply the FDA with the most current evidence so that labels reflect the best scientific information. Congress understands that state tort law is an indispensable partner to federal safety regulation.

As Senator Specter has commented,

> If state law is preempted and lawsuits or claims are dismissed, public safety and health may be affected. In the past, some tort cases have unearthed industry secrets and safety shortcuts that manufacturers have taken. Information obtained in tort suits has turned out to be very useful to regulators seeking to protect the public. In addition, the unearthing of this information has caused manufacturers to improve the safety of their products, or make other changes that protect the public.

Senate Regulatory Preemption Hearing at 133-34.

In addition, the FDA lacks the administrative resources to safeguard drug safety without the assistance of state-court lawsuits. The agency has suffered from politicization and a bias favoring

approval of new pharmaceuticals rather than ensuring the safety of the 11,000 drugs already on the market. As Senator Grassley has observed: "There's enough of a pattern of problematic drugs to ask for an independent review of how the FDA follows up on the effects of medicines that it's approved."[2] One of FDA's own scientific advisory committees has concluded that the agency has "serious scientific deficiencies and is not positioned to meet current or emerging regulatory responsibilities." FDA Subcommittee on Science & Technology, *FDA Science & Mission at Risk* 2-3 (Nov. 2007) ("*FDA Science & Mission at Risk*").

For all these reasons, this Court should hold that the FDCA does not preempt state-law failure-to-warn claims.

ARGUMENT

This Court has instructed that preemption analysis must begin with a healthy presumption against displacement of state law: "In all pre-emption cases, and particularly in those in which Congress has legislated in a field which the States have traditionally occupied, we start with the assumption that the historic police powers of the States were not to be superseded by the Federal Act unless that was the clear and manifest purpose of Congress." *Lohr*, 518 U.S. at 485 (citation, internal quotation marks, and alterations omitted). That starting assumption is fortified in this case by well-settled expectations regarding the impact of the FDCA on state law.

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[2] Associated Press, "FDA's Review Process Under Investigation," Mar. 4, 2008 (available at http://ahrp.blogspot.com/2008/03/gao-to-investigate-fda-review-process.html).

Since the FDCA was enacted in 1938, Congress, the courts, and the FDA have operated with a shared understanding that FDA approval of a drug label does not preempt state-law failure-to-warn claims.

A. The History of the FDCA Confirms That It Does Not Preempt Failure-to-Warn Claims.

Federal drug labeling regulation began with the Pure Food and Drug Act of 1906, Pub. L. No. 59-384, 34 Stat. 768 (1906), codified at 21 U.S.C. §§ 1-15 (1934) (repealed in 1938 by 21 U.S.C. § 329(a)). Prior to 1906, "the States provided the primary and possibly the exclusive source of regulatory control over the labeling of foods and drugs." *In re Vioxx Prods. Liab. Litig.*, 501 F. Supp. 2d 776, 782 (E.D. La. 2007). State courts recognized common-law causes of action for negligence with respect to medicines and related products.[3]

Nothing in the Pure Food and Drug Act of 1906 displaced traditional state-law tort remedies. The Act was part of the progressive agenda of the trust-busting reformer, Theodore Roosevelt,[4] and it was intended solely to protect consumers – not to deny

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[3] *See, e.g., Boyd v. Coca Cola Bottling Works*, 177 S.W. 80, 81 (Tenn.1915); *Willson v. Faxon, Williams & Faxon*, 208 N.Y. 108, 112, 101 N.E. 799, 801 (1913); *Blood Balm Co. v. Cooper*, 83 Ga. 457, 10 S.E. 118, 119 (1889); *Thomas v. Winchester*, 2 Seld. 397, 1852 WL 4748 (N.Y.1852); *Fleet v. Hollenkemp*, 52 Ky. (1 B. Mon.) 219, 220 (1852).

[4] *See* Federal Food and Drugs Act of 1906, Pub. L. No. 59-384, § 3, 34 Stat. 768, 768-69, *repealed by* Federal Food, Drug, and Cosmetic Act of 1938, Pub. L. No. 75-717, § 201(d), 52 Stat. 1040, 1040 (codified in scattered sections of 21 U.S.C.).

state tort remedies to victims of defective drugs.[5] For example, in 1913, this Court considered the effect of a 1907 Wisconsin statute providing that mixtures or syrups offered for sale "shall have upon them no designation or brand ... other than that required by the state law." *McDermott v. Wisconsin,* 228 U.S. 115, 127 (1913). Although this Court held that Wisconsin could not require that federally approved labels "shall be removed from the packages," the Court also "[c]onced[ed] to the state the authority to make regulations consistent with the Federal law for the further protection of its citizens against impure and misbranded food and drugs." *Id.* at 133.

In 1938, after the deaths of more than 100 people from elixir of sulfanilamide, Congress enacted the FDCA, which prohibited false therapeutic claims and for the first time required FDA premarket notification for drugs. As this Court has long recognized, the purpose of the statute was to increase consumer protection. *See United States v. Dotterweich,* 320 U.S. 277, 280, 282 (1943) ("The purposes of this legislation thus touch phases of the lives and health of people which, in the circumstances of modern industrialism, are largely beyond self-protection").

Congress considered including in the Act a private federal cause of action for damages caused by faulty or unsafe products. *See* H.R. Rep. No. 73-6110,

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[5] Dennis R. Johnson, *The History of the 1906 Pure Food and Drugs Act and the Meat Inspection Act,* 37 FOOD DRUG COSM. L.J. 5, 8–9 (1982); Richard Curtis Litman & Donald Saunders Litman, *Protection of the American Consumer: The Muckrakers and the Enactment of the First Federal Food and Drug Law in the United States,* 36 FOOD DRUG COSM. L.J. 647, 648–51 (1981).

pt. 1, § 25 (1933) ("Liability for Personal Injuries - a right of action for damages shall accrue to any person for injury or death proximately caused by a violation of this Act."). Notably, the Senate deleted this proposed private cause of action from the bill on the ground that it was unnecessary because "[a] common-law right of action exists" under state law. *Hearing on S. 1944 Before a Subcomm. of the Comm. on Commerce*, 73d Cong., 2d Sess. 400, 403 (1933). *See also Consumer Fed'n of Am. v. Upjohn*, 346 A.2d 725, 731 (D.C. 1975) (explaining that private right of action was omitted from bill because "it would create an *unnecessary* federal action *duplicative of state remedies*" and concluding that Congress "*rejected* [] setting up a nationally uniform law for such" actions) (emphasis added); Robert S. Adler & Richard A. Mann, *Preemption and Medical Devices: The Courts Run Amok*, 59 MO. L. REV. 895, 924 & n.130 (1994) ("Congress rejected a provision in a draft of the original FD&C Act providing a federal cause of action for damages [for injuries caused by prescription drugs] because 'a common law right of action [already] exists.'").

Congress' assumption that state-law causes of action would remain under the FDCA – coupled with its decision not to provide a federal remedy – is strong evidence that it did not mean to displace traditional state tort actions. Where Congress displaces state law, it typically provides an alternative federal remedy.[6] As the Court has

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[6] *See, e.g.*, 42 U.S.C. § 2210 (Price-Anderson Act); 42 U.S.C. §§ 300aa-10 to 300aa-34 (National Vaccine Injury Compensation Program); 49 U.S.C. § 40101 (Supp. 2004) (Air Transportation Safety and System Stabilization Act of 2001, also known as the

acknowledged, "[i]f Congress had intended to deprive injured parties of a long available form of compensation, it surely would have expressed that intent more clearly." *Bates v. Dow Agrosciences LLC,* 544 U.S. 431, 449 (2005). *See also Silkwood v. Kerr-McGee Corp.,* 464 U.S. 238, 251 (1984) ("This silence [of Congress in enacting and amending the Atomic Energy Act] takes on added significance in light of Congress' failure to provide any federal remedy for persons injured by such conduct. It is difficult to believe that Congress would, without comment, remove all means of judicial recourse for those injured by illegal conduct.").

B. Congress Confirmed Its Understanding In a Series of Amendments To The FDCA.

Congress continued to assume the availability of state-law causes of action in revisiting the FDCA in a series of amendments over the past half-century.

Congress enacted the landmark Kefauver-Harris amendments to the FDCA in 1962, which strengthened pharmaceutical regulation and added further protections for consumers. The purpose of the legislation was "to strengthen and broaden existing laws in the drug field so as to bring about better, safer, medicine and to establish a more effective system of enforcement of the drug laws." S. Rep. No. 87-1744, 87th Cong., 2d Sess. 1 (1962). The catalyst of the reforms was the thalidomide tragedy in Europe in the late 1950s and early 1960s, in which thousands of children were born with birth defects. Institute of

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September 11th Victim Compensation Fund); 29 U.S.C. § 1144 (Employee Retirement Income Security Act of 1974).

Medicine, *The Future of Drug Safety: Promoting and Protecting the Health of the Public* 22, 152 (Alina Baciu, Kathleen Stratton & Shelia P. Burke, eds. 2007) ("IOM Report").

The 1962 Amendments "shifted the burden of proof from FDA (which previously had to prove harm to keep a drug from being marketed) to manufacturers, who now were required to demonstrate both safety and efficacy prior to receipt of marketing approval." IOM Report, *supra*, at 152 (citation omitted). Even with these reforms, the "FDA's ability to form judgments about the safety and efficacy of drugs depends upon the submission of data, usually from drug company sponsors, rather than on the use of data developed independently or on its own initiative." *Id.*

The 1962 Amendments also clarified the FDCA's effect on state law. Congress included language limiting the potential preemptive effect of the FDCA to cases of "direct and positive conflict": "Nothing in the amendments made by this Act to the Federal Food, Drug, and Cosmetic Act shall be construed as invalidating any provision of State law which would be valid in the absence of such amendments unless there is a *direct and positive conflict* between such amendments and such provision of State law." Pub. L. No. 87-781, § 202, 76 Stat. 780, 793 (1962) (emphasis added). The plain language of this provision makes clear that the Amendments do not preempt state law in the absence of such a "direct and positive" conflict.

In contrast, when Congress has wished to preempt state law in the FDCA, it has done so clearly. For example, Congress has enacted an

express preemption provision for medical devices. *Riegel v. Medtronic, Inc.*, 128 S.Ct. 999 (2008) (considering the effect of the express preemption provision of the Medical Device Amendments of 1976, 21 U.S.C. § 360(k)(a)). Although many Members of Congress do not agree with the construction of the Medical Device Amendments adopted by the Court in *Riegel*,[7] that decision does not govern this case because there is no express preemption for drugs in the FDCA.

Further confirming the absence of preemption in this case are the express *anti*-preemption provisions for nonprescription or "over-the-counter" ("OTC") drugs, FDCA Section 751, 21 U.S.C. § 379r, and for the labeling and packaging of cosmetics, FDCA Section 752, 21 U.S.C. § 379s. These provisions prohibit any State or political subdivision from establishing or continuing "any requirement" relating to the regulation of an OTC drug or the labeling or packaging of a cosmetic that is "different from or in addition to, or that is otherwise not identical with," a requirement under the FDCA, the Poison Prevention Packaging Act of 1970, 15 U.S.C. § 1471 *et seq.*, or the Fair Packaging and Labeling Act, 15 U.S.C. § 1451 *et seq.* *See* 21 U.S.C. §§ 379r(a), 379s(a). However, the OTC and cosmetic anti-preemption provisions expressly exempt state product liability actions from federal displacement: "Nothing in this section shall be construed to modify or otherwise affect any action or the liability of any person under the product liability law of any State." 21 U.S.C. §§

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[7] Legislation to reverse the *Riegel* decision has been introduced in both the House and the Senate. *See* S. 3398, 110th Cong.; H.R. 6381, 110th Cong.

379r(e), 379s(e). Thus, although Congress has provided for some degree of preemption for state requirements regarding OTC drugs and cosmetics labeling, it has specifically preserved state-law products liability actions.

The statutory framework demonstrates Congress' clear understanding of the potential for state-law products liability actions against manufacturers of medical devices, OTC drugs, and cosmetics. The absence of any analogous express preemption provision for prescription drugs is significant: "[i]f Congress wants to take the extraordinary step of giving drug manufacturers immunity from personal tort actions, it would expressly state such intentions whether by statute or legislative history." *Merrell Dow Pharms., Inc. v. Oxendine,* 649 A.2d 825, 829 (D.C. 1994) (quoting *Kociemba v. G.D. Searle & Co.,* 680 F. Supp. 1293, 1299-1300 (D. Minn.1988) (ruling that FDCA did not preempt state tort law actions against manufacturers of prescription drugs)).

Moreover, the relationship between OTC and prescription drugs makes the lack of an express preemption provision for prescription drugs even more significant. Some OTC drugs are initially approved as prescription drugs under the FDCA and are "switched over" to OTC status after several years of marketing, as in the cases of Claritin and Zyrtec. Thus, a drug initially receiving FDA approval may later become an OTC drug governed by Section 751, which explicitly contemplates products liability claims under state law. It is implausible to suggest that Congress silently created immunity through federal preemption for prescription-drug-related claims but then affirmatively negated that immunity

when the same drug became OTC. Rather, it is plain that Congress has always assumed that the fact of FDA approval would not preclude state-law product liability actions.

Other provisions of the FDCA also acknowledge Congress' understanding of drug company failure-to-warn liability. For example, Section 756 of the FDCA provides that certain safety reports to FDA may not be considered admissions for liability purposes. 21 U.S.C. § 379v (manufacturer's submission of a safety or adverse event report is not "an admission that the product involved malfunctioned, caused or contributed to an adverse experience, or otherwise caused or contributed to a death, serious injury, or serious illness"). This provision indicates a congressional recognition of the potential for state tort suits, because its evident purpose is to prohibit the use of safety reports in product liability litigation.

In addition, in the National Vaccine Injury Compensation Program ("VICP"), Congress provided an administrative remedy for vaccine related injuries as an alternative to state tort liability, with the possibility of an opt-out to state court if the injured person wishes to pursue a state-law products liability remedy. 42 U.S.C. § 300aa-21(a). Vaccines are approved under the Public Health Service Act, 42 U.S.C. § 300aa-1 to -6, but otherwise regulated as drugs. *E.g.*, 21 C.F.R. § 600 *et seq.* VICP quite clearly confirms Congress' understanding that FDA regulation of a drug does not preempt state-law tort liability.

Given the statutory structure, "[c]ourts have generally rejected the argument that the FDA labeling approval process somehow preempts state

law adequacy of warning claims." *In re Zyprexa Prods. Liab. Litig.*, 489 F.Supp.2d 230, 273 (E.D.N.Y. 2007). Innumerable cases have proceeded to final judgment or settlement on the widespread understanding that FDA approval does not bar state failure-to-warn claims. The traditional view is that "approval by the FDA of the language involved is *not necessarily* conclusive on the question of the adequacy of the warnings." *Brochu v. Ortho Pharm. Corp.*, 642 F.2d 652, 658 (1st Cir. 1981) (emphasis in original; citation omitted). "[C]ompliance with federal laws and regulations concerning a drug, though pertinent, does not in itself absolve a manufacturer of liability." *Salmon v. Parke, Davis & Co.*, 520 F.2d 1359, 1362 (4th Cir. 1975). In *Merrell Dow Pharmaceuticals, Inc. v. Thompson*, 478 U.S. 804, 815-16 & n.13 (1986), this Court encountered a state-law negligence per se claim premised on a violation of the FDCA. *See also Yarrow v. Sterling Drug, Inc.*, 263 F.Supp. 159, 162 (D.S.D. 1967), *aff'd*, 408 F.2d 978 (8th Cir. 1969) (imposing liability "[a]lthough all of the government regulations and requirements have been satisfactorily met in the production and marketing of [the drug], and in the changes made in the literature"); *Stromsodt v. Parke-Davis & Co.*, 257 F.Supp. 991, 997 (D.N.D. 1966), *aff'd*, 411 F.2d 1390 (8th Cir. 1969) ("Although all of the Government regulations and requirements had been satisfactorily met in the production and marketing of Quadrigen, the standards promulgated were minimal. The Defendant still owes a duty to warn of dangers of which it knew or should have known in the exercise of reasonable care."); *Stevens v. Parke, Davis & Co.*, 9 Cal.3d 51, 65, 107 Cal.Rptr. 45, 53, 507 P.2d 653, 661 (1973) ("The warnings required

by such [regulatory] agencies may be only minimal in nature and when the manufacturer or supplier knows of, or has reason to know of, greater dangers not included in the warning, its duty to warn may not be fulfilled."); *Wooderson v. Ortho Pharmaceutical Corp.*, 681 P.2d 1038 (Kan.), *cert. denied*, 469 U.S. 965 (1984) (imposing liability for compensatory and punitive damages based on failure to make a disclosure even though FDA expressly rejected a similar disclosure, proposed by a manufacturer of a competing version of same product); *McEwen v. Ortho Pharmaceutical Corp.*, 528 P.2d 522, 534 (Ore. 1974) ("We hold that the warnings given by an ethical drug manufacturer may be found inadequate," despite FDA approval).[8]

As a former Commissioner of the Food and Drug Administration has written:

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[8] *See also Desiano v. Warner-Lambert Co.*, 467 F.3d 85, 97 & n.9 (2d Cir.2006), *aff'd*, 128 S.Ct. 1168 (2008); *Tobin v. Astra Pharm. Prods., Inc.*, 993 F.2d 528, 537-38 (6th Cir.1993); *Hill v. Searle Labs.*, 884 F.2d 1064, 1068 (8th Cir.1989); *Wells v. Ortho Pharm. Corp.*, 788 F.2d 741, 745-46 (11th Cir.1986); *Alman Bros. Farm & Feed Mill, Inc. v. Diamond Laboratories, Inc.*, 437 F.2d 1295 (5th Cir.1971); *Perry v. Novartis Pharm. Corp.*, 456 F.Supp.2d 678, 685 (E.D.Pa.2006); *Adesina v. Aladan Corp.*, 438 F.Supp.2d 329, 337-38 (S.D.N.Y.2006); *Witczak v. Pfizer, Inc.*, 377 F.Supp.2d 726, 731-32 (D.Minn.2005); *Caraker v. Sandoz Pharm. Corp.*, 172 F.Supp.2d 1018, 1033 (S.D.Ill.2001); *Motus v. Pfizer, Inc.*, 127 F.Supp.2d 1085 (C.D.Cal.2000); *Jones by Jones v. Lederle Labs.*, 695 F.Supp. 700, 709-11 (E.D.N.Y.1988); *Stephens v. G.D. Searle & Co.*, 602 F.Supp. 379, 382 (E.D.Mich.1985); *Savina v. Sterling Drug, Inc.*, 795 P.2d 915, 931 (Kan.1990); *MacDonald v. Ortho Pharm. Corp.*, 394 Mass. 131, 475 N.E.2d 65, 70-71 (1985); *Seley v. G. D. Searle & Co.*, 423 N.E.2d 831, 837 (Oh.1981); *Edwards v. Basel Pharm.*, 933 P.2d 298, 302 (Okla.1997).

> Nothing in the statutes the FDA administers suggests that they oust state damages actions for pharmaceutical products. No appellate court, before or after the advent of the FDA, has held that a state-law failure-to-warn claim for a prescription drug is preempted by federal law. And Congress has not acted to preempt or limit state damage actions, even though it has long been aware of tort litigation over drug products . . . .

David A. Kessler & David C. Vladeck, *A Critical Examination of the FDA's Efforts to Preempt Failure-to-Warn Claims,* 96 GEO. L.J. 461, 462 (2008).

The same view of non-preemption is reflected in the recently enacted Food & Drug Administration Amendments Act of 2007 ("FDAAA"), Pub. L. No. 110-85, 121 Stat. 823 (2007). The Act does not contain any express preemption provision barring state-law damages claims. The sole preemption language included in the FDAAA precludes states and their political subdivisions from "establish[ing] or continu[ing] in effect any requirement for the registration of clinical trials or for the inclusion of information relating to the results of clinical trials in a database," 42 U.S.C. § 282(d), a provision that is not relevant to the instant case.

In enacting the FDAAA, Congress, for the first time, gave FDA the authority to require certain labeling changes. In so doing, however, Congress rejected a Senate proposal sought by pharmaceutical companies that would have required FDA to pre-approve all changes to drug labels – a proposal that might have given drug companies an argument against state tort suits alleging that they wrongly

failed to issue voluntary warnings.[9] Instead of such a provision, Congress adopted a "Rule of Construction" providing that FDA's new labeling change authority "shall not be construed to affect the responsibility" of the manufacturer "to maintain its label in accordance with existing responsibilities, including subpart B of part 201 and sections 314.70 and 601.12 of title 21, Code of Federal Regulations (or any successor regulations)." The cited regulations establish a mechanism for drug manufacturers to provide up-to-date safety information to physicians and patients, even without prior FDA approval. Members of Congress made clear that, in giving FDA the power to order a labeling change, the FDAAA did not alter a manufacturer's longstanding responsibility promptly to update product labels with safety information at the earliest possible moment – without waiting for FDA to approve the change.[10] The statements also

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[9] S. 1082, 110th Cong., 1st Sess. § 208 (proposing new § 506D to FDCA).

[10] As Rep. Waxman explained, "in giving FDA this labeling change authority, Congress is making it clear that we do not intend to impact a drug company's responsibility to promptly update its label with safety information on its own accord." 153 Cong.Rec. H10596 (Sept. 19, 2007) (statement of Rep. Waxman). *Accord*, 153 Cong.Rec. S11833 (Sept. 20, 2007) (statement of Sen. Kennedy) ("Congress has stated very clearly in the legislation that we do not intend the new authority being given to FDA to preempt common law liability for a drug company's failure to warn its customers of health risks."); *id.* at S11834 (statement of Sen. Leahy) ("The legislation we are set to pass today contains a rule of construction making clear that Congress has again decided that we are not preempting State law regarding the responsibility of drug manufacturers to immediately notify consumers of dangers without waiting for the FDA to act."); *id.* at S11835 (statement of Sen. Durbin) ("The drug labeling provisions in today's legislation include a rule of

confirm Congress' intention that, when a manufacturer fails to uphold this responsibility, it should be held accountable under the state tort system, consistent with longstanding practice.

C. The FDA's Longstanding Position Was Consistent With Congress' Understanding.

Until recently, the FDA shared Congress' understanding of the preemptive scope of the FDCA. The FDA has traditionally taken the view that its approval of a drug label does not preempt state laws except in very limited circumstances.

In 1974, for example, FDA adopted a regulation providing for confidential treatment of any identifying information relating to physicians (and other health care professionals) included in adverse drug reaction reports (ADRs) submitted by the manufacturer to the FDA. 21 C.F.R. § 314.80(h). FDA adopted this regulation precisely because it recognized that federal law permits products liability lawsuits in which plaintiffs' counsel would seek such identifying data:

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construction that makes clear that Congress does not intend to preempt state requirements regarding drug companies' responsibilities. Rather, this legislation recognizes that State liability laws, including liability laws for improper drug labeling, play an essential role in ensuring that drug products remain safe and effective for all Americans."). Even those who did not agree with Congress' approach recognized that the FDAAA undermined any argument of preemption. *Id.* at S11837 (statement of Sen. Allard) (expressing disappointment in the Senate's acquiescence to the House language, contained in the Rule of Construction, and warning that it will "open the floodgates" to litigation and is "a definite boon to trial lawyers").

> Large numbers of requests are received from plaintiffs attorneys in product liability lawsuits, requesting records relating to any other injuries caused by the product that is the subject of the lawsuit.

39 Fed. Reg. 44629 (Dec. 24, 1974).

In a 1979 preamble accompanying a drug rule, the agency explained that state tort law does not interfere with federal regulation: "It is not the intent of the FDA to influence the civil tort liability of the manufacturer." 44 Fed. Reg. at 37437 (1979).

Similarly, in a 1998 Final Rule relating to labeling provided directly to patients for certain prescription drugs and other biological products, the FDA indicated that its regulations do not preempt state failure-to-warn claims:

> Some comments contended that the provision of patient labeling would adversely affect the legal liability of manufacturers, physicians, pharmacists, and other prescribers or dispensers of prescription drug products by abrogating the "learned intermediary doctrine." Some comments urged that FDA provide for Federal preemption of State regulation with respect to civil tort liability claims and other labeling requirements. The comment claimed that without preemption, FDA would encourage "failure to warn" claims and challenges to patient labeling, especially compared to professional labeling.
>
> Tort liability cannot be a major consideration for FDA which must be guided

> by the basic principles and requirements of the act in its regulatory activities. Nevertheless, FDA does not believe this rule would adversely affect civil tort liability....
>
> * * *
>
> FDA does not believe that the evolution of state tort law will cause the developments of standards that would be at odds with the agency's regulations.

63 Fed. Reg. 66378, 66384 (1998). FDA added that its regulation providing for FDA approval of patient labeling for a limited number of products was "not intended to preclude the states from imposing additional labeling requirements." *Id.*

In 1986, a former chief counsel of the FDA explained the agency's view that federal approval did not bar state failure-to-warn claims:

> In a number of cases, state and federal courts have held that package inserts approved by FDA have contained inadequate disclosure of risks. ... Is not such review under state law a violation of the supremacy of federal law? Are not manufacturers being held liable for inserts controlled not by them but by FDA, so that juries are imposing on manufacturers disclosure obligations inconsistent with the regulation of inserts by FDA? The answer currently is no. In some situations, FDA has not, at the relevant time, considered the precise question of whether the insert it had previously approved should be changed in light of subsequent information. Where that is the case, there would seem to be no

> relevant federal decision entitled to supremacy. Nor does the Food, Drug, and Cosmetic Act reflect a congressional intent to preempt in all circumstances common law review of drug labeling.

Richard M. Cooper, *Drug Labeling & Products Liability: The Role of the Food and Drug Administration*, 41 FOOD DRUG & COSM. L.J. 233, 234-35 (1986).

Another chief counsel of the FDA explained that this Court's no-preemption ruling in *Lohr* was consistent with the FDA's "longstanding ... presumption against preemption." Margaret Jane Porter, *The* Lohr *Decision: FDA Perspective and Position*, 52 FOOD & DRUG L.J. 7, 10 (1997). She added that:

> Given the harsh implications of foreclosing all judicial recourse for consumers injured by defective medical devices, FDA does not believe that Congress intended to effect so sweeping change without even a comment. Rather, the agency believes that Congress intended to restrict preemption to positive enactments (for example, legislation or regulations) that apply to the marketing of medical devices within a state, and did not intend to preempt state tort remedies for injury to individual consumers.

Id. at 9. Although the article concerned medical devices specifically rather than pharmaceuticals, its explanation of FDA's longstanding view of limited preemption applies *a fortiori* with respect to drugs. After all, the FDCA contains no express preemption

provision for drugs, in contrast to the Medical Device Act amendments interpreted in *Medtronic*.

In December 2000, the FDA proposed a new regulation to address the form and content of drug labeling, the principal purpose of which was to require a "Highlights" section on drug labels. At that time, the agency explained that "this proposed rule does not preempt state law," and "FDA has determined that this proposed rule does not contain policies that have federalism implications or that preempt State law." 65 Fed. Reg. 81082, 81103 (2000).

In 2006, in finalizing these labeling rules, the agency took a different view with respect to the *very same regulation*, claiming that the federal approval of drug labeling may preempt a state tort claim based on a failure to warn:

> FDA believes that under existing preemption principles, FDA approval of labeling under the act, whether it be in the old or new format, preempts conflicting or contrary State law.

71 Fed. Reg. 3922, 3934 (2006). FDA added:

> State law actions also threaten FDA's statutorily prescribed role as the expert Federal agency responsible for evaluating and regulating drugs.

Id. at 3935.

The preemption preamble is an improper FDA power grab that seeks to seize authority belonging to Congress, the States, and the courts. The FDA did an inexplicable about-face and attempted to achieve

federal preemption "through the back door." *Zyprexa*, 489 F.Supp.2d at 275-76. "Until January 24, 2006, the FDA itself had consistently recognized that state-law claims could coexist with federal regulation of prescription drugs. Indeed, the FDA's current position on preemption represents a significant departure from well-settled administrative and judicial views on the issue, and ultimately is both unpersuasive and untenable . . . ." *In re Vioxx Prods. Liab. Litig.*, 501 F. Supp. 2d 776, 788 (E.D. La. 2007).

The 2006 preemption preamble is also inconsistent with Executive Order No. 13132, which requires federal agencies to consult with state and local officials whenever a proposed rule contains preemption provisions. The FDA failed to follow the prescribed procedures in 2006. *See Senate Regulatory Preemption Hearing* at 6-7 (statement of Hon. Donna Stone, Del. State Rep. and President, National Conference of State Legislatures). Accordingly, the Conference of State Chief Justices adopted a resolution in January 2008 stating that "recent actions by federal agencies have led to a growing concern by the Conference of Chief Justices about federal regulatory agency efforts to preempt federal and state statutes and common law through the promulgation of proposed rules."[11]

Even assuming that it would be proper for a court to defer to an agency on the issue of a statute's preemptive effect – an issue which this Court has not resolved[12] – the FDA's new-found position does not

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[11] Available at http://ccj.ncsc.dni.us/FederalismResolutions/resol1RespectPrinciplesOfFederalism.html.

[12] *Smiley v. Citibank*, 517 U.S. 735, 744 (1996); *see also Medtronic, Inc. v. Lohr*, 518 U.S. 470, 512 (1996) (O'Connor, J.,

deserve judicial deference. In fact, in *Riegel v. Medtronic, Inc.*, 128 S. Ct. 999 (2008), this Court did not rely upon the agency's view of the preemptive effect of the Medical Device Amendments. Instead, this Court opined that "the degree of deference might be reduced by the fact that the agency's earlier position was different." *Id.* at 1009. This Court has repeatedly held that an agency's change of position is not entitled to deference. *See, e.g., Bates v. Dow Agrosciences LLC*, 544 U.S. 431, 449 (2005); *Norfolk Southern Ry. Co. v. Shanklin*, 529 U.S. 344, 356 (2000); *Good Samaritan Hosp. v. Shalala*, 508 U.S. 402, 418 (1993) (citing *INS v. Cardoza-Fonseca*, 480 U.S. 421, 446, n.30 (1987)).

Further features of the 2006 preemption preamble preclude *Chevron* deference. Because the proposed rule had stated that *no* preemption would arise from the labeling requirement, the public received no notice or opportunity to comment against preemption. The 2000 preamble had addressed preemption not as a subject for comment, but as part of the analysis of the labeling rule itself and whether it ought to be changed because of liability concerns. The 2000 preamble, in other words, presupposed the potential for liability under state law and did not even hint that federal preemption was on the horizon. *See* Content and Format of Labeling for Human Prescription Drugs and Biologics, 65 Fed. Reg. at 81103 (2000). The drafters of the 2006 preamble proceeded from precisely the opposite premise, denying fair notice and an opportunity for interested parties to comment. The absence of public comment

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concurring in part and dissenting in part, joined by Rehnquist, C.J., and Scalia and Thomas, JJ.).

precludes any claim of deference. *See United States v. Mead Corp.*, 533 U.S. 218, 231 (2001) (denying deference because, among other reasons, the agency ruling was "far removed . . . from notice-and-comment process").

Next, the 2006 preemption statement arose in the context of a regulatory preamble. Under FDA regulations, a preamble to a proposed or final regulation is merely "an advisory opinion," rather than part of the rule itself. 21 C.F.R. § 10.85(d)(1). "An advisory opinion may be amended or revoked at any time after it has been issued," without notice or comment. *Id.* at § 10.85(g). "An advisory opinion may be used in administrative or court proceedings to illustrate acceptable and unacceptable procedures or standards, but not as a legal requirement." *Id.* at § 10.85(j). If an advisory option is not binding in administrative or court proceedings, it cannot be entitled to *Chevron* deference. *See Long Island Care at Home, Ltd. v. Coke*, 127 S.Ct. 2339, 2349 (2007) (agency guideline entitled to only "persua[sive]" rather than "bind[ing]" weight); *Gonzales v. Oregon*, 546 U.S. 243, 256-57 (2006) (interpretive rule not entitled to deference); *Mead*, 533 U.S. at 232 ("interpretive rules ... enjoy no *Chevron* status *as a class*"); *Martin v. Occupational Safety and Health Review Comm'n*, 499 U.S. 144, 157 (1991) (interpretive rules are "not entitled to the same deference as norms that derive from the exercise of the Secretary's delegated lawmaking powers"). *See also Shalala v. Guernsey Memorial Hospital*, 514 U.S. 87, 99 (1995) ("interpretive rule" "do[es] not require notice and comment").

In sum, the FDA's 2006 change of position provides no basis for upsetting Congress' longstanding understanding of the preemptive effect of the FDCA. The FDA's abrupt change in view should be rejected.

D. This Court Should Not Upset Congress' Settled Expectations.

Congress, the FDA, and the courts have long assumed the availability of state-law damages actions for failure-to-warn and inadequate warning claims, notwithstanding FDA approval of a drug label. To find preemption in this context would eliminate all compensation for often devastating injuries – lost wages, medical costs, and other traditional forms of damages – without providing any federal remedy as a substitute. It would effectively bestow an immunity on drug manufacturers that Congress has refused to grant.

Moreover, a holding of preemption would also have serious implications for institutional principles arising from the separation of powers. Agencies, as creatures of their organic statutes, do not have the power to regulate with the force of law unless Congress has delegated that power to them. *See Gonzales*, 546 U.S. at 255-56. Deference is warranted only "when it appears that Congress delegated authority to the agency generally to make rules carrying the force of law, and that the agency interpretation claiming deference was promulgated in the exercise of that authority." *Mead*, 533 U.S. at 226-27.

Congress has not authorized the FDA to imbue the 2006 preamble with preemptive force. To defer to the FDA's preemption preamble would turn the

proper inquiry upside down. Preemption is ultimately a question of congressional intent, not agency intent. *Medtronic,* 518 U.S. at 485. An agency may not expand the preemptive reach of a statutory scheme outside the congressional mandate. *See Adams Fruit v. Barrett*, 494 U.S. 638, 650 (1990) (declining to defer to agency's view regarding preemptive reach of federal statute's right of action, and noting that, despite agency's authority to issue relevant safety standards, "an agency may not bootstrap itself into an area in which it has no jurisdiction.") (quoting *Federal Maritime Comm'n v. Seatrain Lines, Inc.*, 411 U.S. 726, 745 (1973)).

In addition, important issues of repose and settled statutory meaning counsel strongly against overturning decades of practice under the FDCA. Where Congress, the FDA and the courts have all operated on the basis of a common, longstanding view regarding the construction of a statutory scheme, there are powerful reasons not to disrupt their shared interpretation. The expectations regarding the preemptive effect of the FDCA reflect precisely the kind of "well-embedded interpretation" of a statute that this Court has held is entitled to judicial respect. *CBOCS West,* 128 S.Ct. at 1958.

The value of repose in this context is akin to the principle of statutory *stare decisis.* This Court has explained that it "give[s] great weight to *stare decisis* in the area of statutory construction," in part because of "institutional concerns about the relationship of the Judiciary to Congress." *Neal v. United States,* 516 U.S. 284, 295 (1996) (Kennedy, J.). *See also Hohn v. United States*, 524 U.S. 236, 251 (1998) ("Considerations of *stare decisis* have special force in

the area of statutory interpretation . . . .") (quoting *Patterson v. McLean Federal Credit Union*, 491 U.S. 164, 172-73 (1989)); *Quill Corp. v. North Dakota*, 504 U.S. 298, 320 (1992) (Scalia, J., concurring in part and in the judgment) (stressing importance of *stare decisis* in dormant Commerce Clause context, where Congress "has the final say over regulation of interstate commerce").

For more than 70 years, Congress has operated against the background understanding that FDA approval of a drug label does not bar state-law failure-to-warn claims. If that rule of law is to be altered, it should be changed directly by Congress. This Court should not nullify more than 70 years of practice under the FDCA by bestowing an immunity that Congress has thus far declined to grant, nor should it permit the FDA to accomplish such a result indirectly through an unauthorized expansion of its regulatory power.

E. Preemption Would Disrupt The Congressional Drug Safety Scheme

The congressionally designed scheme for drug safety contemplates a meaningful role for state-law tort actions. When a drug is approved, the available information is not sufficient to guarantee its safety over time. FDA typically approves drugs on the basis of relatively small clinical trials, which may involve healthy volunteers and other subjects far different from the patients for whom doctors usually write prescriptions. The Institute of Medicine of the National Academies reports that drugs are generally tested on no more than 600 to 3,000 patients prior to approval. *See* IOM Report, *supra*, at 36. At the time of approval the label contains only the information

that can be definitively established by the trials. Thus, "FDA approval does not represent a lifetime guarantee of safety and efficacy," and drugs enter the U.S. market with "incomplete safety profiles." *Id.* at 2, 37. Because of statistical limitations, latency periods, and population sub-groups with special characteristics, pre-approval testing cannot reveal the safety problems that may emerge only after long-term, large-scale use. The IOM concluded:

> Preapproval trials typically are too small to detect even significant safety problems if they are rare. An adverse event (even a serious one) that occurs in less than one in 1,000 patients cannot be reliably detected except in the largest premarket trials but can pose a serious public health problem when hundreds of thousands or millions of people use the drug.

IOM Report at 37-38 (citations omitted).

Many features of drug testing, production and marketing can result in new and unexpected risks once a drug enters widespread use, and these dangers are often solely within a manufacturer's knowledge. As a matter of both resources and statutory responsibility, manufacturers are in a far better position than FDA to discover unexpected risks of their own drugs and to make appropriate warnings to patients. FDA oversees the safety of 12,000 drugs made by 5,000 manufacturers around the world. Given the agency's limited resources and information, it is utterly unrealistic to expect that the FDA alone – with no assistance from state tort suits – can protect patients from the post-market risks of even a fraction of these products.

The voluntary physician reporting system on which FDA relies for collecting real-time information on drug side effects identifies fewer than 1% of serious side effects.[13] Moreover, FDA's system for collecting and analyzing those reports is severely antiquated, underfunded, and often overwhelmed, resulting in "incredible missed opportunities" to detect signals of post-market drug risks. *FDA Science & Mission at Risk* at 50 & App. J. A long series of congressional hearings and reports has documented that the FDA's resources are not commensurate with the agency's enormous task.[14] One of FDA's own advisory committees concluded that "[i]n contrast to previous reviews that warned crises would arise if funding issues were not addressed, recent events and our findings indicate that some of those crises are now realities and American lives are at risk." *FDA Science & Mission at Risk* at 6. The committee documented a litany of FDA shortcomings:

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[13] FDA Medwatch, The Clinical Impact of Adverse Event Reporting (Oct. 1996). http://www.fda.gov/medwatch/articles/medcont/postrep.htm#und

[14] *See, e.g., Risk and Responsibility: The Roles of the FDA and Pharmaceutical Companies in Ensuring Safety of Approved Drugs, Like Vioxx: Hearing Before the House Comm. on Government Reform*, 109th Cong. (2005); *FDA's Drug Approval Process: Up to the Challenge?: Hearing Before the Senate Comm. on Health, Educ., Labor and Pensions*, 109th Cong. (2005); *FDA, Merck and Vioxx: Putting Patient Safety First?: Hearing Before the Senate Comm. on Finance*, 108th Cong. (2004); U.S. GOV'T ACCOUNTABILITY OFFICE, DRUG SAFETY: IMPROVEMENT NEEDED IN FDA'S POSTMARKET DECISION-MAKING AND OVERSIGHT PROCESS 10, *available at* www.gao.gov/cgi-bin/getrpt?GAO-06-402.

> We found that FDA's resource shortfalls have resulted in a plethora of inadequacies that threaten our society - including, but not limited to, inadequate inspections of manufacturers, a dearth of scientists who understand emerging new technologies, inability to speed the development of new therapies, an import system that is badly broken, a food supply that grows riskier each year, and an information infrastructure that was identified as a source of risk in every Center and program reviewed by the Subcommittee. We conclude that FDA can no longer fulfill its mission without substantial and sustained additional appropriations. . . .

Id. at 2.

The FDAAA of 2007 is intended to address these deficiencies, but it is not a panacea. Even with the enactment of the 2007 amendments, "drugs with unrecognized toxicity will reach the market." Bruce M. Psaty & David Korn, *Congress Responds to the IOM Drug Safety Report - In Full,* 298 JAMA 2185, 2187 (Nov. 14, 2007). Senator Kennedy, chief Senate sponsor of the FDAAA and a leader on federal drug regulation for decades, has explained that even a strengthened FDA should not be expected to assume exclusive responsibility for collecting and analyzing post-market safety data:

> Clearly, the resources of the drug industry to collect and analyze postmarket safety data vastly exceed the resources of the FDA, and no matter what we do, they will always have vastly greater resources to monitor the safety of their products than the FDA does. It is

> absurd to argue that the FDA, even with the enhanced resources and authorities provided by this legislation, commands the field when it comes to postmarket safety. The drug companies have the capacity to do a far more comprehensive job . . . [and] cannot be allowed to ignore their responsibilities and wait for the FDA to act.

153 Cong. Rec.S11832 (daily ed. Sept. 20, 2007).

By necessity, manufacturers play a central role in the development and dissemination of information about their products. Accordingly, cases brought by injured consumers under state law can help ensure that manufacturers have the incentive to provide the most up-to-date warning information. Gregory Curfman, executive editor of the New England Journal of Medicine, recently warned that "preemption of common-law tort actions against drug and medical device companies is ill advised and will result in less safe medical products for the American people." *House FDA Preemption Hearing* (testimony of Dr. Curfman). Another expert advised a House Committee that:

> Preempting lawsuits against pharmaceutical manufacturers would remove a check on pharmaceutical manufacturers that is essential to prescription drug safety and the public health. Without the possibility of litigation against manufacturers and their executives, we are likely to see greater misrepresentation of safety-related data and more inappropriate use of potentially harmful medications.

Id. (testimony of Aaron S. Kesselheim, Brigham & Women's Hospital and Harvard Medical School).

State tort cases also provide an invaluable source of data for regulators. Time and time again, problems with long-term use of drugs were identified first in failure-to-warn litigation, involving such drugs as Vioxx, Bextra, Celebrex, Avandia, Rezulin, Baycol, Halcion, and Zomax. State court litigation plays the same complementary role in the FDCA context as it does in other areas. *See Bates,* 544 U.S. at 451 ("Private remedies that enforce federal misbranding requirements would seem to aid, rather than hinder, the functioning of FIFRA."); *CSX Transp., Inc. v. Easterwood,* 507 U.S. 658, 668 (1993) (railroad safety); *Hillsborough County v. Automated Medical Laboratories, Inc.,* 471 U.S. 707, 720-21 (1985) (blood plasma).

Moreover, it is clear from the brief *amicus curiae* of the United States in this case ("SG Br.") that in fact there is no conflict between FDA approval of a label and state-law failure-to-warn duties. The Solicitor General explains that, under the FDA's regulations, a manufacturer may make changes in drug labeling by first submitting a supplemental application to the FDA. SG Br. 3. A manufacturer is *required* to submit such a supplemental application "to include a warning about a clinically significant hazard as soon as there is reasonable evidence of a causal association with a drug." 21 C.F.R. § 201.57(c)(6). FDA labeling regulations instruct that drug "labeling shall be revised to include a warning as soon as there is reasonable evidence of an association of a serious hazard with a drug...." *Id.* at §§ 201.57(e), 201.80(e).

The Solicitor General adds that a manufacturer may "change a drug's labeling after its supplemental application is received by FDA, *without waiting for the agency's approval of the change*, if, among other things, the change 'add[s]' or 'strengthens' a warning or a statement about administration of the drug in order to promote safety." SG Br. 3 (emphasis added and quoting 21 C.F.R. § 314.70(c)(6)(iii)(A) and (C)). However, an FDA proposed rule would permit changes without prior approval "only to address 'newly discovered risks' for which there is sufficient evidence of causal association with the drug." *Id.* at 4.

In the view of the undersigned Members of Congress, the FDA's current regulations appropriately require manufacturers to warn of risks as early as possible – regardless of whether the risk is "newly discovered" or not. In any event, even if prior FDA approval for labeling changes to enhance safety were required, such a requirement could not possibly shield a manufacturer from liability (if it could have any preemptive effect at all) when the drug maker had never even requested the approval. In addition, manufacturers may provide risk information by various means *besides* label changes, such as "Dear Health Care Professionals" letters. 21 C.F.R. § 200.5; 44 Fed. Reg. 37434, 37447 (1979). A manufacturer's failure to use such non-label measures may serve as a basis for imposing state-law failure-to-warn liability.

In sum, there is no basis for reversing 70 years of statutory interpretation and preempting traditional state-law failure-to-warn claims.

CONCLUSION

The judgment below should be affirmed.

Respectfully submitted,

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IN THE

Supreme Court of the United States

WYETH,

Petitioner,

v.

DIANA LEVINE,

Respondent.

ON WRIT OF CERTIORARI
TO THE SUPREME COURT OF VERMONT

BRIEF FOR *AMICUS CURIAE* THE NATIONAL COALITION AGAINST CENSORSHIP IN SUPPORT OF RESPONDENT

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INTEREST OF THE *AMICUS*[1]

The National Coalition Against Censorship (NCAC), founded in 1974, is an alliance of 50 national nonprofit organizations, including religious, educational, professional, artistic, labor, and civil rights groups united in the conviction that freedom of thought, inquiry and expression are indispensable to a healthy democracy. Among NCAC's projects is The Knowledge Project: Censorship & Science, which educates the public and policy-makers about the importance of safeguarding the free exchange of information about scientific research and developments. The Knowledge Project advocates for greater transparency in government decision-making about science, and for the public's right to know non-classified scientific information, especially when that information implicates public health and welfare. Because the issues in this case relate to the ability of the public to receive truthful information about the risks of pharmaceuticals beyond that which is disclosed on FDA-approved labels, participation as *amicus* in this case falls squarely within NCAC's mission. The positions advocated by the NCAC in this brief do not necessarily reflect the positions of each of its participating organizations.

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[1] Petitioners and Respondents have filed blanket consents to the submission of *amicus* briefs with this Court. No counsel for a party authored this brief in whole or in part, and no such counsel or party made a monetary contribution intended to fund the preparation or submission of this brief. No person other than *amicus curiae*, or its members, or counsel, made a monetary contribution to its preparation or submission.

INTRODUCTION

The question in this case is whether conflict preemption principles preclude imposition of liability against the defendant under state tort law. Defendant Wyeth argues that Food and Drug Administration ("FDA") regulations prevented it from issuing more robust warnings about its drug, Phenergan, than those approved by the FDA. Wyeth asserts that because it could not comply with both state law (requiring more robust warnings) and federal law (precluding more robust warnings, absent FDA approval), conflict preemption prevents imposition of state tort failure-to-warn liability.

There are a number of bases for rejecting Wyeth's contention that state tort law is preempted by FDA regulations. These include: The basic presumption against preemption; the power of a drug company pursuant to 21 C.F.R. section 314.70(c) to issue additional warnings without pre-approval by the FDA; the fact that there is no evidence in the record that the FDA considered, let alone rejected, a proposed label that would have fulfilled Wyeth's state tort duties; and others. These issues were all carefully considered by the Vermont Supreme Court in its opinion and are addressed in other principal and *amici* briefs. This brief is intended to focus on one narrow aspect of Wyeth's conflict preemption argument: Wyeth's First Amendment right (whether actually exercised or not) to provide additional truthful warnings about the risks of its product, over and above the warnings contained in the label approved by the FDA.

State police powers designed to protect citizens' health and safety afford Vermont (and every other state) the power to impose liability on manufacturers for failing to adequately warn about the dangers of their products. *Medronic v. Lohr*, 518 U.S. 470, 485, 116 S.Ct. 2240, 135 L.Ed.2d 700 (1996). Absent some impediment in federal law that otherwise ***precludes*** such a warning, there can be no federal preemption of those state police powers.

Nothing in the Food, Drugs and Cosmetics Act ("FDCA") ***precluded*** Wyeth from issuing additional warnings, even without FDA approval. *See* 21 C.F.R. section 314.70(c). But even if there were, in fact, such a statutory preclusion, it would be trumped by Wyeth's right and power under the First Amendment to issue additional truthful warnings about the risks of the "IV push" administration of Phenergan. Conflict preemption principles cannot apply in the first instance if there is no ***valid*** federal law that is in conflict with state law. Because the First Amendment gave Wyeth the ***power*** to issue additional truthful warnings, and state law imposed the ***duty*** to do so, there is no conflict between state and federal law.

LEGAL ARGUMENT

WYETH HAD THE RIGHT, UNDER THE FIRST AMENDMENT, TO PROVIDE MORE ROBUST WARNINGS AND COULD, THEREFORE, COMPLY WITH STATE LAW REQUIREMENTS THAT IT DO SO.

Wyeth's basic argument in this case (see Petitioner's Principal Brief, pp i, 12-39) is that because the FDA controls the content of pharmaceutical drug labels, including the warning information, Wyeth could not comply with both federal law (which dictated the permitted warnings) and state law (which required more robust warnings). As such, Wyeth argues, it could not comply with both federal and state law, thereby invoking conflict preemption principles to preclude application of state tort liability principles.

The fundamental problem with Wyeth's argument is its premise that it could not provide more robust warnings without violating FDA regulations against "misbranding." That assertion is patently untrue in light of Wyeth's First Amendment right to disseminate truthful statements about its product – including truthful warnings about the danger of using it as an "IV push." The drug industry agrees: The First Amendment right to provide truthful information about pharmaceuticals has long been the industry's own rallying cry for the manufacturers' right to promote the off-label use of FDA-approved drugs.

A. The First Amendment protects the right of drug companies to make truthful statements about their products.

Warnings about the risk of use of drugs is pure speech. Warnings are not given in order to enhance the sale of the product. Rather, warnings tend to limit product sales and, as such, do not fall within the ambit of "commercial" speech. Because FDA regulations applied as argued by Wyeth would be a content-based restriction on Wyeth's First Amendment right to speak, they must pass the strict scrutiny test. *United States v. Playboy Entertainment Group, Inc.*, 529 U.S. 803, 813, 120 S.Ct. 1878, 146 L.Ed.2d 865 (2000), *U.S. v. Grace*, 461 U.S. 171, 103 S.Ct. 1702, 75 L.Ed.2d 736 (1983).

But even if warnings were considered to be commercial speech, Wyeth's interpretation of FDA regulations violates the First Amendment. This Court has already held that the FDCA and FDA regulations must comport with the Free Speech Clause of the First Amendment under *Central Hudson Central Hudson Gas & Elec. Corp. v. Public Serv. Comm'n of N.Y.*, 447 U.S. 557, 566, 100 S.Ct. 2343, 65 L.Ed.2d 341(1980). *Thompson v. Western States Medical Center*, 535 U.S. 357, 365, 122 S.Ct. 1497 (2002).

(1) More robust warnings than those contained in the FDA label constitute pure, not commercial, speech and are subject to the most extensive First Amendment protection.

Wyeth's argument that FDA regulations prohibit additional truthful warnings is a content-based restriction on speech and, as such, must meet strict scrutiny requirements. *United States v. Playboy Entertainment Group, Inc.*, 529 U.S. 803, 813, 120 S.Ct. 1878, 146 L.Ed.2d 865 (2000), *U.S. v. Grace*, 461 U.S. 171, 103 S.Ct. 1702, 75 L.Ed.2d 736 (1983).

Whether a given communication constitutes commercial speech is predicated on "the commonsense distinction between speech proposing a commercial transaction . . . and other varieties of speech." *Bolger v. Youngs Drug Products Corp.*, 463 U.S. 60, 64, 103 S.Ct. 2875, 77 L.Ed.2d 469 (1983). In *Bolger*, this Court identified three factors to use in determining whether speech is "pure" speech or commercial speech: (1) Whether the speech is concededly an advertisement; (2) Whether the speech refers to a specific product; and, (3) Whether the speaker has an economic motivation for disseminating the speech. *Bolger*, at 66. If ***all three factors*** are present, the speech may properly be characterized as commercial speech. *Id.*; *see, also, Washington Legal Foundation v. Friedman*, 13 F.Supp.2d 51, 64 (D.D.C. 1998) ("*WLF I*"), *appeal dism'd*, 202 F.3d 331 (D.C. Cir. 2000).

On a common sense level, a more robust warning of the risks of an approved drug does not comport with

the *Bolger* test for commercial speech. After all, an advertisement "calls public attention to [the product], especially by emphasizing desirable qualities so as to arouse desire to buy or patronize." *WLF I*, 13 F.Supp.2d at 64. A warning about the excessive risks in using an approved drug in a particular manner does exactly the opposite: It ***de***emphasizes the desirable qualities of the drug and is necessarily intended to suppress the use of the drug. Similarly, a warning that highlights the risk of using a drug is an economic ***dis***incentive, and does not comport with the third Bolger factor because there is no economic motivation for disseminating the speech.

Because more robust warnings about the use of an approved drug are "pure" (as opposed to "commercial") speech, any content-based restriction is subject to the strict scrutiny standard. *Sable Communications of California, Inc. v. F.C.C.*, 492 U.S. 115, 126, 109 S.Ct. 2829, 106 L.Ed.2d 93; *Playboy, supra*, 529 U.S. at 813-814. Where a statute regulates speech based on content, the statute "must be narrowly tailored to promote a compelling government interest." *Playboy*, at 813. Moreover, to the extent Wyeth argues that it could not disseminate more robust and truthful warnings about the use of its product ***without prior FDA approval*** because of FDA labeling requirements, such a limitation would amount to a "prior restraint" on protected expression – which is the most serious and least tolerable infringement on First Amendment rights. *See, Organization for a Better Austin v. Keefe*, 402 U.S. 415, 419, 91 S.Ct. 1575, 29 L.Ed.2d 1 (1971); *see also, The Florida Star v. B.J.F.*, 491 U.S. 524, 533, 109 S.Ct. 2603, 105 L.Ed.2d 443 (1989).

It would be irrational to conclude that the FDA has a compelling governmental interest in keeping physicians and patients in the dark about the risks associated with the drugs they are using. Such a conclusion would, in fact, be directly contrary to the FDA's mandate that it promote and enhance consumer ***safety***. *United States v. Dotterwiech*, 320 U.S. 277, 282, 64 S.Ct. 134, 88 L.Ed. 48 (1943); see also *Cartwright v. Pfizer, Inc.*, 369 F.Supp.2d 876, 886 (E.D. Tex. 2005); *Witczak v. Pfizer, Inc.*, 377 F.Supp.2d 726, 732 (D. Minn. 2005) ("The primary purpose of both the FDCA and FDA's regulatory scheme is to protect the public.") The First Amendment assures that truthful speech that makes the use of drugs ***safer*** cannot be limited by the FDA's regulatory scheme.

To hold that Wyeth was prohibited from issuing truthful information regarding safety risks essentially concludes that the public should be kept in the dark regarding information that impacts their health and safety and that such information cannot be disclosed until the government (through the FDA) has had an opportunity to authorize or bless the message. This kind of content-based restriction on information is the type of evil the First Amendment was meant to safeguard against. *Washington Legal Foundation v. Henney*, 56 F.Supp.2d 81, 85 (D.D.C.,1999) ("*WLF III*") ("The First Amendment is premised upon the idea that people do not need the government's permission to engage in truthful, nonmisleading speech about lawful activity.") As such, a strict scrutiny analysis belies Wyeth's argument that it could not provide more robust warnings about the use of Phenergan as an IV push.

(2) Even If It Were Deemed Commercial Speech, Wyeth Has A First Amendment Right To Issue Truthful Warnings.

Even if additional warnings are deemed "commercial speech," Wyeth has a First Amendment right to issue *truthful* warnings and to publish *truthful* facts about its drug and the risks of using it. *Thompson v. Western States Medical Center*, 535 U.S. 357, 365, 122 S.Ct. 1497 (2002). In *Western States*, this Court struck down a ban on advertising unapproved compounded drugs in the FDA Modernization Act of 1997 (FDAMA). The Court applied the commercial speech test of *Central Hudson Gas & Electric Corp. v. Public Serv. Comm'n*, 447 U.S. 557 (1980). Thus, this Court asked: (1) whether the speech was untruthful or misleading, or concerned unlawful activity (characteristics that would strip the speech of First Amendment protection and end the analysis); (2) whether the Government had asserted a "substantial" interest in restricting the speech; (3) whether the Government had demonstrated that the restriction "directly advanced" such a substantial interest; and (4) whether the Government had established that the restriction was "not more extensive than is necessary to serve that interest." *Western States*, 535 U.S. at 365.[2]

[2] This Court also clarified some ambiguities in past cases concerning the "final prong" of the commercial speech analysis, holding that "if the Government could achieve its interests in a manner that does not restrict speech, or that restricts less speech, the Government must do so." *Id.*, at 1506. This Court emphasized that "[i]f the First Amendment means anything, it means that regulating speech must be a last -- not first — resort." *Id.*, at 1507.

a. Issuing Warnings Is Neither Unlawful Nor Inherently Misleading

As factually determined by the jury in this case, truthful additional warnings about the use of Phenergan were necessary for the protection of the plaintiff's health and safety. Wyeth has argued that it could not issue such warnings without first obtaining the FDA's approval, essentially contending that only the FDA can determine if the warning is *truthful*. Wyeth's principal brief, pp 40-45. But numerous cases have explicitly rejected the proposition that speech is "inherently misleading" because it does not satisfy government requirements.

In *Pearson v. Shalala*, 164 F.3d 650, 655 (D.C. Cir.), *reh'g denied*, 172 F.3d 72 (D.C. Cir. 1999), the FDA contended that the health claims appellants wished to include on dietary supplements were inherently misleading because they did not meet FDA's requirement that there be "significant scientific agreement" about such claims before they could be included in the labeling for dietary supplements. The appellate court disagreed, finding the argument that health claims were inherently misleading unless they satisfied FDA's significant scientific agreement requirement "almost frivolous." 164 F.3d at 655. The court even concluded that the claims at issue had the potential to mislead, but that FDA failed to prove that the problem could not be cured through disclosures rather than an outright ban on the claims. *Id.* at 655-60.

In the context of prescription drugs, the theory that statements lacking FDA approval were inherently misleading was considered and rejected in *WLF I*.

There, the FDA argued that manufacturer-funded or manufacturer-disseminated speech about off-label uses is inherently misleading because the FDCA "prescribes a specific system for determining the 'truth' of claims about drugs and devices." *WLF I*, 13 F. Supp.2d at 67. The court concluded that FDA had no power to impose a "specific system for determining truth," holding that:

> In asserting that any and all scientific claims about the safety, effectiveness, contraindications, side effects and the like regarding prescription drugs are presumptively untruthful or misleading until the FDA has had the opportunity to evaluate them, FDA exaggerates its overall place in the universe.

Id.

The *WLF I* court went on to hold that scientific conclusion are "*not untruthful or inherently misleading merely because the FDA has not yet had the opportunity to evaluate the claim. Id.* Cases decided outside of the FDA context have reached the same conclusions about the government's power to dictate truth. In *Bioganic Safety Brands, Inc. v. Ament*, 174 F. Supp.2d 1168 (D. Colo. 2001), for example, the State of Colorado argued that safety claims about pesticides were inherently misleading because a Colorado statute banned such claims. The court found otherwise, rejecting the theory that the State could properly

determine that safety claims on pesticide labels were inherently misleading as a matter of law":

> Whether speech is "inherently misleading" . . . is a determination for the court, not the legislature, to make. If a legislature could place speech outside First Amendment protection by simply declaring the speech "inherently misleading," the First Amendment . . . would be subject to *de facto* modification by state legislatures.

Id. at 1180.[3]

In short, Wyeth cannot sustain a position that truthful warnings regarding the danger of using Phenergan in an "IV push" context is inherently

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[3] For additional cases, *see, e.g.*, *Peel v. Attorney Reg. & Disciplinary Commission*, 496 U.S. 91, 108, 110 S.Ct. 2281, 110 L.Ed.2d 83 (1990) ("[w]hether the inherent character of a statement places it beyond the protection of the First Amendment is a question of law over which Members of this Court should exercise *de novo* review"); *Nutritional Health Alliance v. Shalala*, *953* F. Supp. 526, 529 (S.D.N.Y. 1997), *aff'd in part, vacated and dismissed in part on other grounds*, 144 F.3d 220 (2d Cir. 1998) ("[a]lthough the Government argues that health claims that have not been FDA approved are inherently misleading, not all potential health claims are misleading; at least some can be presented in a non-misleading fashion"); *Ass'n of Nat'l Advertisers, Inc. v. Lungren*, 809 F. Supp. 747, 756 (N.D. Cal. 1992), *aff'd*, 44 F.3d 726 (9th Cir. 1994) ("[i]f First Amendment scrutiny in the commercial speech arena is to have any bite at all, a legislative body cannot justify its restrictions on commercial speech simply by declaring that marketing claims are misleading").

misleading unless it complies with FDA requirements. Such a position would nullify the constitutional protections accorded to commercial speech, and the cases have squarely rejected this sort of "*de facto* modification" of the First Amendment. Simply put, government-mandated systems for determining truth are not a part of our First Amendment jurisprudence.

b. While the FDA May Have A "Substantial Interest" In Protecting The Health and Safety of Citizens, It Cannot Restrict Truthful Information Out of Fear That it May be Misused

It is not disputed that government agencies may seek to regulate speech for certain legitimate purposes — perhaps most importantly in the FDA context, to prevent the serious harms that can result from *untruthful* speech. Whether speech is categorized as commercial or non-commercial, a restriction designed to prevent citizens from using ***truthful*** information to make choices about lawful activities does not satisfy this requirement. The First Amendment "directs us to be especially skeptical of regulations that seek to keep people in the dark for what the government perceives to be their own good." 44 *Liquormart, Inc. v. Rhode Island*, 517 U.S. 484, 503, 116 S.Ct. 1495, 134 L.Ed.2d 711 (1996).

This principle has been recognized repeatedly in cases involving restrictions on information about drugs and devices, including this Court's first decision extending First Amendment protection to commercial

speech. In that case, *Virginia State Bd. of Pharmacy v. Virginia Citizens Consumer Council, Inc.*, 425 U.S. 748, 769, 96 S.Ct. 1817, 48 L.Ed.2d 346 (1976), the State of Virginia argued that a ban on advertising prescription drug prices was justified by the fear "that if the pharmacist who wishes to provide low cost, and assertedly low quality, services is permitted to advertise, he will be taken up on his offer by too many unwitting customers." This Court disagreed, holding at 770 that:

> Virginia is free to require whatever professional standards it wishes of its pharmacists. . . . But it may not do so by keeping the public in ignorance of the entirely lawful terms that competing pharmacists are offering. . . . [T]he justifications Virginia has offered for suppressing the flow of prescription drug price information, far from persuading us that the flow is not protected by the First Amendment, have reinforced our view that it is. We so hold.

Similarly, the court in *WLF I* rejected paternalism as a valid basis for restricting the dissemination of truthful information about off-label uses of drugs and devices, holding that "[t]o the extent that the FDA is endeavoring to keep information from physicians out of concern that they will misuse that information, the regulation is wholly and completely insupportable." *WLF I*, 13 F. Supp.2d at 69. "If there is one fixed principle in the commercial speech arena," the court observed, "it is that 'a State's paternalistic assumption that the public will use truthful, nonmisleading commercial information unwisely cannot justify a decision to

suppress it.'" *Id.* at 69-70 *quoting 44 Liquormart, Inc. v. Rhode Island*, 517 U.S. 484, 497 (1996).[4]

In *Western States*, this Court rejected the theory that an interest in protecting patients from truthful information could justify its suppression. There, the Court addressed the argument that FDAMA's ban on advertising compounded drugs could be sustained by an interest in preventing patients who do not need compounded drugs from seeking them, holding that:

> Even if . . . FDAMA's speech-related restrictions were motivated by a fear that advertising compounded drugs would put people who do not need such drugs at risk by causing them to convince their doctors to prescribe the drugs anyway, that fear would fail to justify the restrictions. Aside from the fact that this concern rests on the questionable assumption that doctors would prescribe unnecessary medications . . . [it] amounts to a fear that people would make bad decisions if given truthful information about compounded drugs. . . . We have previously rejected the notion that the Government has an interest in preventing the dissemination

[4] This analysis, of course, wholly undermines Wyeth's argument that the FDA's approval process must be upheld in order to avoid "over warning," i.e., giving so many warnings that physicians will simply ignore ***all*** the warnings. That "paternalistic assumption" that physicians will not heed the warnings if too many are given "cannot justify a decision" to suppress truthful warnings.

> of truthful commercial information in order to prevent members of the public from making bad decisions with the information.

Western States, 535 U.S. at 374.

Other courts have similarly held that "[t]he First Amendment mandates that we presume that speakers, not the government, know best both what they want to say and how to say it." *Riley v. Nat'l Fed'n of Blind, Inc.*, 487 U.S. 781, 790 91, 108 S.Ct. 2667, 101 L.Ed.2d 669 (1988). In fact, "[t]he very purpose of the First Amendment is to foreclose public authority from assuming a guardianship of the public mind through regulating the press, speech, and religion." *Thomas v. Collins*, 323 U.S. 516, 545, 65 S.Ct. 315, 89 L.Ed. 430 (1945) (Jackson, J., concurring). "To this end, the government, even with the purest of motives, may not substitute its judgment as to how best to speak for that of speakers and listeners; free and robust debate cannot thrive if directed by the government." *Riley*, 487 U.S. at 791. Accordingly, in light of the foregoing authority, the FDA could not prevent Wyeth from issuing truthful warnings regarding the use of Phenergan in an "IV push" mode.

c. The Purported Restrictions on Speech Do Not Advance the Government's Substantial Interest in Protecting the Health and Safety of Consumers

This Court has repeatedly confirmed that the role of the FDCA and the FDA is to protect consumers. *F.D.A. v. Brown & Williamson Tobacco Corp.*, 529 U.S. 120, 120 S.Ct. 1291, 146 L.Ed.2d 121 (2000) ("The labeling requirements currently imposed by the FDCA . . . require the FDA to regulate the labeling of drugs and devices to protect the safety of consumers."); *United States v. Sullivan*, 332 U.S. 689, 696, 68 S.Ct. 331, 92 L.Ed. 297 (1948) ("[T]he Act as a whole was ***designed primarily to protect consumers from dangerous products***." [Emphasis added].).

This intent is also reflected in the FDA's regulations. Prior to 1965, the FDA expressly prohibited drug companies from strengthening the warnings in their drug labels without ***prior*** FDA approval. 25 Fed.Reg. 12,592, 12,595 (Dec. 9, 1960.) In 1965, however, the FDA recognized the importance of incentivizing drug companies to warn of additional risks when appropriate, and to do so without the FDA's pre-approval. 30 Fed.Reg. 993 (Jan. 30, 1965).

In light of the fact that the FDCA's primary objective is to protect consumers, that objective and interest would not be advanced by accepting Wyeth's contention that the FDA could or should prohibit a ***truthful*** warning about the use of its product. *See, e.g., United States v. Dotterweich*, 320 U.S. 277, 282 (1943);

see also Cartwright, 369 F.Supp.2d at 886; *Witczak*, *supra*, 377 F.Supp.2d at 732. The more information a physician has when prescribing a drug, the better. *See*, American Medical Association, *Reporting Adverse Drug and Medical Device Events: Report of the AMA's Council on Ethical and Judicial Affairs*, 49 Food & Drug Law Journal 359, 363 (1994) ("The purpose of any requirement to disseminate knowledge is to benefit patients and advance their level of care."). Even Professor Hall, a spokesperson for the Washington Legal Foundation, acknowledges that "[b]etter information provided faster to patients and physicians will presumably lead to better healthcare decisions." Ralph F. Hall, *The Risk of Risk Reduction: Can Postmarket Surveillance Pose More Risk Than Benefit?*, 62 Food & Drug L.J. 473, 479 (2007). An FDA restriction limiting the distribution of truthful warnings would undermine FDA's interest in promoting access to reliable scientific and medical information and would thereby endanger the lives of patients who are prescribed medications.

This Court's First Amendment jurisprudence has long mandated that government cannot suppress truthful information that would aid consumers — even when that information does nothing more than allow them to make better ***financial*** judgments about what they buy. *Virginia State Bd. of Pharmacy v. Virginia Citizens Consumer Council, Inc.*, 425 U.S. 748, 96 S.Ct. 1817, 48 L.Ed.2d 346 (1976); *44 Liquormart, Inc. v. Rhode Island*, 517 U.S. 484, 116 S.Ct. 1495, 134 L.Ed.2d 711 (1996); *Thompson v. Western States Medical Center*, 535 U.S. 357, 365, 122 S.Ct. 1497 (2002). It is far more important that these First Amendment principles apply

to assure that patients and their physicians have truthful information that will assist them in choosing drug products that affect consumers' health and safety and not merely their pocketbooks. An FDA regulation that limits the dissemination of truthful warnings undermines patient safety, is contrary to governmental intent and violates the First Amendment.

d. A Restriction On Warnings Is More Extensive than Necessary

Finally as to the fourth factor, Wyeth's contention that the FDA does or should bar all additional warnings until approved by the FDA is more extensive than necessary since it burdens substantially more speech than necessary. *U.S. v. Edge Broadcasting Co.*, 509 U.S. 418, 430, 113 S.Ct. 2696, 125 L.Ed.2d 345 (1993). First, as already noted, such a restriction would be an unnecessary and unconstitutional prior restraint. *See, e.g., WLF II*, 56 F.Supp.2d at 85. Second, as the *WLF I* court noted, in lieu of prohibiting speech, the FDA could require "full, complete, and unambiguous disclosure by the manufacturer." *WLF I*, 13 F.Supp.2d at 73. Finally, as the *WLF I* court noted, the FDA cannot restrict the dissemination of truthful information, especially when the "truthful information may be life saving information." *WLF I*, 13 F.Supp.2d at 73. Truthful warnings are exactly the type of life-saving information that cannot be restricted and is fully protected by the First Amendment.

The FDA has long understood that completely suppressing the exchange of accurate scientific and medical information between physicians and the

manufacturers of drugs and devices does not serve its public health objectives. For example, the FDA stated in 1994 that, "because the agency recognizes the importance of dissemination of reliable scientific information . . . , it has developed a number of policies related to dissemination of such information." 59 Fed. Reg. 59820, 59822 (Nov. 18, 1994). In its most recent pronouncement on this issue, the FDA confirmed that manufacturers have a right to "disseminate truthful and non misleading medical journal articles and medical or scientific reference publications on unapproved uses of approved drugs...to healthcare professionals." *See* FDA Guidance for Industry, available at *http://www.fda.gov/oc/op/ goodreprint.html*, at p. 3. The FDA further held that, along with the dissemination of such information, the manufacturer should also disclose "***any significant risks or safety concerns known to the manufacturer*** . . ." *See id.*, at p. 6. Thus, contrary to Wyeth's contention, Wyeth was not only permitted but ***encouraged*** to disclose any known safety problems with its drug. For this reason alone, Wyeth's preemption argument should be rejected.

Accordingly, under the First Amendment, Wyeth had a right to issue truthful additional warnings about the risks of using Phenergan in an IV push.

(3) As the industry itself vociferously argues, the First Amendment permits drug manufacturers to provide truthful information about their products in addition to the FDA-approved drug label.

As Professor Ralph F. Hall, writing for the Washington Legal Foundation, stated in December 2005, "[f]or more than a decade, the pharmaceutical industry, the Food and Drug Administration ("FDA") and the courts have struggled to integrate FDA's regulation of off-label promotion of drugs [fn omitted] with the First Amendment's protection of free speech." WLF, "Legal Backgrounder," Vol. 20, No. 59, December 2, 2005, available at *www.wlf.org/upload/120205LBHall.pdf*, most recently accessed on 8/11/08. The Washington Legal Foundation has been very active on behalf of the industry in convincing courts that the FDA's power over the contents of a drug's label does not impair a drug company's right to promote its products' off-label use through the publication and dissemination of scientific articles. *See, e.g., WLF I*; *WLF II*; *WLF II*); *Washington Legal Foundation v. Henney*, 128 F.Supp.2d 11 ("*WLF V*"). In the *Freidman* litigation, the Washington Legal Foundation actually obtained a permanent injunction against the FDA to stop it from initiating enforcement actions against drug makers who provided truthful scientific studies to physicians about their drugs' off-label uses. The FDA's appeal of that injunction was dismissed as "moot" because the FDA agreed that the First Amendment precluded such enforcement actions. *Washington Legal Foundation v. Friedman*, 202 F.3d 331, 335-337 (D.C. Cir. 2000) ("*WLF IV*").

As recently as April 21, 2008, the Washington Legal Foundation concluded that this series of cases stand for the proposition that the FDA cannot regulate truthful statements by a drug company about its products, in whatever venue or context, and that the FDA's proposed regulatory guidance on off-label communications with physicians not only violates the injunction issued against the FDA on these issues, but generally violates the First Amendment as well. *See Comments of The Washington Legal Foundation to the Food and Drug Administration Department of Health & Human Services Concerning Draft Guidance for Industry on Good Reprint Practices in Response to the Public Notice Published at 73 Fed. Reg. 9342 (February 20, 2008)*, dated April 21, 2008, pp 11-17, available at *http://www.wlf.org/upload/Reprints%20Guidance-%20WLF%20Comments.pdf*, last accessed on 8/9/08. ("Comments.")

Washington Legal Foundation's focus in its litigation against the FDA and in its Comments is the First Amendment right of drug manufacturers to disseminate scientific studies supporting the use of an FDA-approved drug for treatment of a condition for which the drug has not yet been approved by the FDA. But as Professor Hall explains, "[o]ff-label speech involves ***any*** discussion about a product's uses, ***safety***, or efficacy that is outside of the FDA-approved labeling." (*Id.*, at p. 2; emphasis added.) Thus, the WLF's arguments that the First Amendment precludes the FDA's regulation of a manufacturer's dissemination of truthful information about its drugs applies with equal force irrespective of whether the information relates to additional uses for the drug ("off-label" uses) or more robust warnings about risks associated with the use of the drug.

This was also recently the conclusion of Daniel Troy, the Chief Counsel to the FDA from 2001-2004, in a published response in the New England Journal of Medicine to a prior article advocating for limits on the promotion of off-label uses of approved drugs. As Mr. Troy stated, that article "dramatically understate[d] the robust, sound constitutional protection the U.S. Supreme Court affords truthful, nonmisleading commercial communication such as that embodied in reprints of scientific articles discussing off-label uses." *New England Journal of Medicine*, July 31, 2008, p. 536. Further, Mr. Troy stated, "[a]ppropriate off-label use that informs proper patient care is fostered by more, not less, communication of truthful, nonmisleading information." *Id.*

Thus, as the industry itself argues, dissemination of truthful, nonmisleading warnings that are not otherwise contained in the FDA-approved drug label is speech protected by the First Amendment.[5]

[5] The truth of scientific information about the risks associated with drugs naturally would be tested as those products enter the marketplace and are used by consumers. If, as a result, the public begins to doubt the completeness and accuracy of manufacturers' statements about drug risk, individuals would be able to seek accurate information through state product liability actions. Recourse to the courts increases the incentives for manufacturers to disclose truthful information, informs the public of any previously undisclosed risks, and helps cure deficiencies in the FDA's approval and post-marketing review process.

B. To avoid constitutional doubts, the statute and regulation should be interpreted to allow drug companies to issue additional warnings.

Statutes, and the regulations drafted pursuant to them, must be interpreted so as to avoid constitutional doubts. *Miller v. French*, 530 U.S. 327, 336, 120 S.Ct. 2246, 147 L.Ed.2d 326 (2000); *Almendarez-Torres v. U.S.*, 523 U.S. 224, 237-238 118 S.Ct. 1219, 140 L.Ed.2d 350 (1998); *Communications Workers of America v. Beck*, 487 U.S. 735, 761-762, 108 S.Ct. 2641, 101 L.Ed.2d 634. Drug manufacturers have recently argued that while 21 C.F.R. section 314.70 allows them to add or strengthen a warning without prior FDA approval, they may only utilize that regulation when the additional warning is based on "newly discovered" evidence. In other words, the industry argues, if they have long known about the problem, section 314.70(c) does not permit them to issue a different warning, absent FDA approval.

First, the plain text of the regulation in no way supports that argument. On its face, section 314.70(c)(6)(iii)(A) permits a drug manufacturer to "add or strengthen a contraindication, warning, precaution, or adverse reaction" at any time. The regulation only requires that the FDA have *received* — not ruled on — a proposed supplemental change to the label. There is nothing in the text of the section that supports the conclusion that there must be "newly discovered" evidence supporting the change.

More importantly, construing the regulation in that manner violates the rule that a regulation must be

construed in a manner that resolves any doubt ***against*** unconstitutionality. Construction of the regulation in the manner suggested by the industry raises constitutional concerns to the extent it would prohibit dissemination of truthful information of hazards that have long been known, but secreted by the manufacturer for whatever reason. Such a construction of the regulation would be invalid under the First Amendment.

C. Because Wyeth had a First Amendment right to issue more robust warnings about its product than those contained in the FDA-approved label, it could comply with state law requiring those more robust warnings.

Wyeth's challenge to the Vermont Supreme Court's decision is predicated solely on principles of conflict preemption. Wyeth asserts that it could not comply with both federal law (which, Wyeth contends, precluded more robust warnings) and state law (which required more robust warnings).

But, as demonstrated, the First Amendment provided Wyeth with the right and power to disseminate truthful warnings about the use of its drug that were more robust than those contained in the FDA-approved label, regardless of whether it chose to exercise that power. Because federal law did not restrict the warnings Wyeth could issue, Wyeth could have complied with state law and issued more warnings, had it chosen to do so. There was no conflict and, hence, no conflict preemption.

It is anticipated that Wyeth will argue in response to this brief that even if the First Amendment ***allowed***

Wyeth to issue additional warnings about its drug, the First Amendment also allows it to remain silent. The problem with that argument, however, is that it ignores the context: This brief is in response to Wyeth's assertion that it ***couldn't*** legally issue additional warnings without the FDA's approval. But the First Amendment says it could. It is not the First Amendment that ***requires*** Wyeth to issue further warnings. It only ***permits*** it to do so. It is state law which imposes the duty. The point is that the state law duty is not in conflict with any federal limitation because, in fact, there is no federal limitation.

The question is this: Can a manufacturer with knowledge of a grave risk associated with its drug issue a warning to the medical community regarding that risk? Wyeth claims that federal law prohibits it from issuing such a warning. Wyeth is wrong. Wyeth was aware of the substantial risks of using Phenergan in an IV push mode. Wyeth had both a state law duty and a First Amendment right to issue a warning regarding that risk without waiting for the FDA's confirmation of the appropriateness of the warning. Wyeth was not put to the test of choosing between compliance with state law requiring the warning and federal law precluding the warning, because the federal regulations purportedly precluding the warning violated Wyeth's First Amendment right to give it. Wyeth could, therefore, comply with both federal and state law.

CONCLUSION

First Amendment jurisprudence requires rejection of Wyeth's argument that it could not issue additional truthful warnings about its product.

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WYETH,

Petitioner,

v.

DIANA LEVINE

Respondent.

On Writ of Certiorari to the Supreme Court of Vermont

BRIEF OF THE NATIONAL CONFERENCE OF STATE LEGISLATURES AS *AMICUS CURIAE* SUPPORTING RESPONDENTS

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INTEREST OF THE *AMICUS CURIAE*

Amicus, the National Conference of State Legislatures, represents State Legislatures throughout the United States.[1] State governments, and their legislatures, as independent branches of co-equal States in our system of Federalism, are deeply involved in the creation of State tort laws. As such, State Legislatures have been on the front line of the policy decisions about "Tort Reform." In some cases, this involvement has included drafting, holding extensive hearing on, and either passing bills which enact similar preemption rules to that recently advocated by the Federal Executive Branch in its "Preamble;" or, in other instances, rejecting such rules of preemption. At least 40 States have enacted comprehensive statutes to govern products liability claims and recoveries by their citizens. Given the substantial and sustained exercise of State authority in the area of State tort law since the enactment of the Constitution, *Amicus* has a substantial interest in opposing policy statements – like that recently made by the executive branch through the FDA's preamble – that attempt to seize, without the involvement of Congress and the normal legislative process, and through circumvention of Executive Or-

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[1] The parties have consented to the filing of this brief. No counsel for a party authored this brief in whole or in part, and no counsel or party made a monetary contribution intended to fund the preparation or submission of this brief. No person other than *amicus curiae*, its members, or its counsel made a monetary contribution to its preparation or submission.

der 13132 "Federalism" (8/4/1999), entire areas of State authority.

Moreover, the question of whether a federal agency can, without a grant of authority to preempt from Congress, dictate preemption as a matter of agency policy has significant fiscal implications for State governments. Consumers' injuries do not simply vanish, nor are they magically healed, when the claims are preempted. Instead, the costs of their injuries are paid by insurers, borne by the individuals themselves, and, if the injured consumers cannot pay and are uninsured, State governments may pay (in whole, or with matching federal funds) for medical expenses and disability payments. These and other social costs, and the countervailing impact on States' economies of consumer litigation, have been the focus of much debate and legislation in the States. This vital decision-making process is a key part of our cooperative system of Federalism, and one which *Amicus* has a direct interest in preserving.

STATEMENT OF THE CASE

A. Federalism and Executive Order 13132

Executive Order 13132, aptly titled "Federalism" (Aug. 4, 1999), recognized that "the States possess unique authorities, qualities, and abilities to meet the needs of the people and should function as laboratories of democracy." *Id.*, at § 2(c).[2]

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[2] Executive Order 13132 incorporates and expands on Executive Order 12612 (October 26, 1987), 52 Fed. Reg. 41685,

The Executive Order states that "[n]ational action limiting the policymaking discretion of the States shall be taken only where there is constitutional and statutory authority for the action and the national activity is appropriate in light of the presence of a problem of national significance." *Id.*, at § 3(b).

Section Four of the Executive Order outlines several "Special Requirements for Preemption." This section requires, *inter alia*, that federal agencies restrict to the minimum level necessary any regulatory preemption of State law (§ 4(c)); that federal agencies shall consult *prior to* publication of an NPRM with appropriate State and local officials in an effort to avoid the possibility of conflict between State law and federal interests (§ 4(d)); and that "when an agency proposes to act through adjudication or rulemaking to preempt State law, the agency shall provide all affected State and local officials notice and an opportunity for appropriate participation in the proceedings" (§4(e)).

The Executive Order further requires that "no agency shall promulgate any regulation that has federalism implications and that preempts State law, unless the agency, prior to the formal promulgation of the regulation . . . consulted with State and local

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3 C.F.R. (1987) Corp., p. 252, which remained in effect from 1987 till it was updated in 1999 with Executive Order 13132. Both orders required similar pre-notice of proposed rulemaking, consultation, and notification, and respect for State policy decisions.

officials early in the process of developing the proposed regulation;" (§ 6(c)(1)).

The mandatory language of this Executive Order applies to federal agencies under 44 U.S.C. § 3502(1) that are not considered to be independent regulatory agencies, as defined in 44 U.S.C. § 3502(5). Section Nine states that "[i]ndependent regulatory agencies are encouraged to comply with the provisions of this order." The FDA is not identified by name in either 44 U.S.C. § 3502(1) or 44 U.S.C. § 3502(5), but is not deemed to be an independent regulatory agency because it is a subdivision of the Department of Health and Human Services. The mandatory language of the Executive Order thus applies to the FDA.

B. The FDA's prior position and 2000 statement that preemption was not implicated by the new labeling rule.

When Congress enacted the Food, Drug, and Cosmetic Act ("FDCA") in 1938, it specifically rejected a proposal to include a federal private right of action for damages because Congress recognized that such actions already existed under state common law. *See generally, In re Paxil Lit.*, No. CV 01-07937, 2002 WL 31375497 at *1 (C.D. CA 2002) (Pfaelzer, J.) (discussing and citing legislative history); Adler & Mann, *Preemption and Medical Devices: The Courts Run Amok*, 59 Mo. L. Rev. 895, 924 & n.130 (1995). In 1962, when Congress passed amendments to the FDCA, it added a provision specifically stating that "[n]othing in the amendments made by this Act to the Federal Food, Drug, and Cosmetic Act shall be construed as invalidating any provision of State law

which would be valid in the absence of such amendments unless there is a direct and positive conflict between such amendments and such provision of State law." Pub. L. No. 87-781, 76 Stat. 780, 793 (1962). Accordingly, consistent with the legislative mandate, for nearly 40 years the FDA has, prior to the current Administration, consistently taken the position that its labeling requirements represent *minimum standards* which do not preempt state law.[3]

In 1977, when the FDA revised the patient package insert for oral contraceptives, it stated that "whether particular labeling may alter a manufacturer's liability in a given instance cannot be considered as a dispositive factor by the Commissioner." 42 Fed. Reg. 37636, 37637 (1977). Two years later, the FDA declared that "[i]t is not the intent of the FDA to influence the civil tort liability of the manufacturer." 44 Fed. Reg. 37434, 37447 (1979). The agency has historically and consistently recognized, in harmony with the Executive Order, that product liability litigation asserting State law claims serves

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[3] Rather than discuss in detail the regulatory scheme, *Amicus* directs the Court to an Article by Former FDA Commissioner David A. Kessler, who was appointed by President George H.W. Bush, and reappointed by President William J. Clinton., which discusses in detail the FDA's prior positions and internal competence as these relate to drug labeling. *See* Kessler, D.A. and Vladeck, D.C., *A Critical Examination of the FDA's Efforts to Preempt Failure-To-Warn Claims*, 96 Geo. L.J. 461 (2008)

an important role in protecting the public. *See, e.g.*, 44 Fed. Reg. at 37447 (*citing McEwen v. Ortho Pharms. Corp.*, 528 P.2d 522 (Ore. 1974)). In doing so, the FDA acknowledged that compliance with agency labeling requirements does not supplant state tort doctrines, such as the manufacturer's continuing duty to warn of risks as they are discovered, noting that "drug labeling does not always contain the most current information and opinion available to physicians about a drug because advances in medical knowledge inevitably precede formal submission of proposed new labeling by the manufacturer and approval by FDA." *Id.* at 37435. Thus, "[c]ommunication of significant medical information should be encouraged, not restricted," and "the addition to labeling and advertising of additional warnings ... is not prohibited by [FDA's] regulations." *Id.*

In 1998, while issuing regulations addressing pharmacists' provision of written patient information ("Medication Guides") for certain types of prescription drugs, the FDA stated once again that its regulations established only *minimum standards* which posed no actual or anticipated conflict with state law, and which are not intended to preclude the imposition of additional labeling requirements. 63 Fed. Reg. 66378, 66384 (1998). Even though Medication Guides are subject to intense regulatory oversight by the FDA, *see* 63 Fed. Reg. 66378, the FDA reaffirmed its anti-preemption stance, and rejected comments from the pharmaceutical industry calling for the preemption of state labeling requirements, stating that "FDA regulations establish the minimal standards necessary, but were not intended to preclude states

from imposing additional labeling requirements. States may authorize additional labeling but they cannot reduce, alter, or eliminate FDA-required labeling." 63 Fed. Reg. at 66384.

The FDA took the same position in 2000 when it published its proposed drug labeling rule – the same rule now before this Court – declaring as follows:

> FDA has analyzed this proposed rule in accordance with Executive Order 13132: Federalism. The Order requires Federal agencies to carefully examine actions to determine if they contain policies that have federalism implications or that preempt State law....
>
> FDA is publishing this proposed rule to revise its regulations governing the format and content of labeling for human prescription drug products.... ***[T]his proposed rule does not preempt State law.***
>
> ***Accordingly, FDA has determined that this proposed rule does not contain policies that have federalism implications or that preempt State law.***

65 Fed. Reg. 81082, 81103 (2000) (emphasis added).

Having expressly stated that the proposed new labeling rules did not have federalism implications or preempt State law, the FDA did not seek or receive

comments on the Federalism implication of preemption.[4]

C. The FDA's Change in Position

In 2001 a new Chief Counsel of the FDA, Daniel Troy, was appointed. Mr. Troy had represented pharmaceutical and other industries in lawsuits against the FDA. *See generally,* Schultz, S., *Mr. Outside Moves Inside: Daniel Troy fought the FDA for years; now he's helping to run it. U.S. News and World Report* (Aug. 7, 2008) (http://health.usnews.com/usnews/health/articles/030324/24fda.htm). Once Appointed, Mr. Troy publicly called for industry representatives to suggest cases in which the FDA could advocate for preemption. *See generally*, O'Reilly, J.T., *U.S. Food and Drug Regulation in Its First Century and Beyond*, 93 Cornell L. Rev. 939, 953-4 (July 2008). The FDA Subsequently began filing amicus briefs whose arguments mirrored the opinions expressed in the FDA's current preamble. No such position had ever been advocated in the over 90-year history of the FDA.[5] However,

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[4] In its Amicus Brief the United States has ignored this history, instead simply repeating the incorrect statement of the preamble itself that it was purportedly the "long standing view" of the FDA that its labeling regulations preempted state law as they were both a floor and a ceiling, while asserting that the preceding 65+ year record of FDA reaffirmation of nonpreemption are mere "snippets."

[5] While the FDA claimed it had filed four amicus briefs supporting preemption, none supported any type of field pre-

courts rejected the agency's argument. E.g., *In re Paxil Litigation*, 2002 WL 31375497 (C.D. Cal. Oct. 18, 2002); *Witczak v. Pfizer*, 377 F. Supp. 2d 726 (D. Minn. 2005); *Cartwright v. Pfizer*, 369 F. Supp. 2d 876 (E.D. Tex. 2005); *McNellis v. Pfizer, Inc.*, 2005 WL 3752269 (D. N.J. Dec. 29, 2005); *Zikis v. Pfizer, Inc.*, 2005 WL 3019409 (N.D. Ill. Nov. 8, 2005). *Peters v. AstraZeneca, L.P.*, 417 F. Supp. 2d 1051, 1056-57 (W.D. Wis. 2006); *Madden v. Wyeth, Inc.*, No. 3-03-CV-0167-BD, 2005 U.S. Dist. Lexis 19989, at *10 n.6 (N.D. Tex. Sept. 14, 2005); *Albertson v. Wyeth, Inc.*, 2003 Pa. Dist. & Cnty. Dec. Lexis 135, at *18-25 (Pa. C.P. July 8, 2003); *Caraker v. Sandoz Pharms. Corp.*, 172 F. Supp. 2d 1018 (S.D. Ill. 2001).

At the end of the day on December 30, 2005, the Executive Branch Liaison for *Amicus*, Susan Frederick, received a call from FDA intergovernmental staff. *Affidavit of Susan Parnas Frederick*, at 1 (attached hereto). The staffer told Ms. Frederick that the FDA planned to finalize its long-dormant labeling rule in early January 2006 and would be includ-

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emption based upon regulation. *See* Zieve, A.M., and Wolfman, B., *The FDA's Argument for Eradicating State Tort Law*, Toxics Law Reporter (BNA) Vol. 21, No. 21 (5/25/06) available at http://www.citizen.org/documents/PDFARTIC.pdf). Moreover, the FDA's brief to this Court in *Buckman v. Plaintiffs' Legal Comm.*, 2000 WL 1364441, at *17 (filed Sept. 13, 2000), cited by the FDA directly acknowledged, contrary to the FDA's current position, "the historic primacy of state regulation of matters of health and safety" and the appropriateness of a presumption against preemption of state-law claims *including* failure to warn claims. *Id.*

ing a statement preempting state laws. Ms. Frederick immediately asked, on behalf of the NCSL, to be placed in touch with FDA's general counsel's office, for a copy of the proposed "policy statement," for the consultation process under Executive Order 13132 to occur, and for the Notice and comment period to be re-opened. *Id.*

Ms. Frederick then received a call from the FDA's general counsel's office, and, as she states in her Affidavit:

> I was informed by Mr. Randy Luttig that NCSL could not review this proposed language in advance of its publication, that this telephone call constituted the consultation under Executive Order 13132, and that the comment period was closed and would not be reopened to permit NCSL to submit comments on the new language.
>
> In a follow-up conversation with FDA staff, I was informed that the FDA considers the requirement of Executive Order 13132 satisfied, and was again told I would not be able to review a copy of the proposed "policy statement." I subsequently learned that FDA had received and accepted numerous late, non-public, comments from industry on the proposed regulation.

Id. at 1-2.

Thereafter, with no further rule making or public notice, the FDA simply attached a "preamble" to its January 24, 2006 Final Rule on labeling which had

not, prior to its publication, seen the light of day. The FDA, attempting to explain away its failure to follow the requirements of Executive Order 13132, *see* 71 Fed. Reg. 3922, § 10, explained as follows:

> FDA sought input from all stakeholders on new requirements for the content and format of prescription drug labeling through publication of the proposed rule in the Federal Register. ***Although the proposed rule did not propose to preempt state law, it did solicit comment on product liability issues.*** FDA received no comments on the proposed rule from State and local governmental entities.

Id. (emphasis added). Those from whom the FDA supposedly "did solicit comment" were not further described or identified. With this as its only justification, the FDA stated that it "believes that it has complied with all of the applicable requirements under Executive Order 13132 and has determined that this final rule is consistent with the Executive Order." *Id.*[6]

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[6] In its submission to this Court, the United States claims the FDA's preamble is entitled to "substantial deference" yet fails to further explain or justify the FDA's failure to follow Executive Order 13132, or its inappropriate treatment of state and local interests under the Executive Order, the very behavior that divests the preamble of any entitlement to due deference.

Shortly after the FDA published its preamble, ranking members of both chambers of Congress wrote to the FDA strongly objecting to the agency's preamble comments. *See* Letter to Michael O. Leavitt from Edward M. Kennedy and Christopher J. Dodd (February 23, 2006) and Letter to Michael O. Leavitt from Henry A. Waxman, John D. Dingell, and Sherrod Brown (February 23, 2006) (http://dodd.senate.gov/index.php?q=node/3381). The legislators sharply criticized the FDA for attempting to "reverse[] a long-standing FDA policy of permitting complementary State activities intended to protect consumers from unsafe drugs." They also noted the fact that "neither affected state and local entities, nor the general public were given an opportunity to comment" because the FDA "provided no opportunity for dissenting views to be heard." (*Id.*) Finally, the legislators attacked the very foundation of the FDA's analysis, which abrogates the roles and powers of the legislative and judicial branches, accusing the FDA of relying on "misleading characterizations of the governing statute and irrelevant cases, while ignoring contrary legislative history." (*Id.*)

Amicus voiced similar objections, stating in a formal letter to the Secretary of Health and Human Services that the FDA's 180 degree shift in position, combined with its refusal to go through the legally required notice and comment process, constituted "an abuse of agency process and a complete disregard for our dual system of government.... It is unacceptable that FDA would not permit the states to be heard on language that has a direct impact on state civil justice systems nationwide." Letter to Mike Leavitt

from Steven J. Rauschenberger Assistant Senate Minority Leader, Illinois President, NCSL (January 13, 2006) (http://www.ncsl.org/programs/press/2006/060113leavitt.htm).

The FDA has come under increasing fire, from the medical profession itself (a constituency with undoubted relevant expertise), for its inability, through lack of funding and otherwise, effectively to regulate the products of pharmaceutical laboratories and safeguard the public health. Whether or not such criticism is invariably warranted, the FDA is unquestionably without the legal authority or expertise to regulate, much less nullify, the legislative and judicial products of the States' laboratories of democracy.[7] Announcements of preemption made without expertise, authority, or due process merit no deference.

As noted by Former Commissioner Kessler, subsequent to the FDA's issuance of the preamble, Congress passed and the President signed the FDA Amendments Act of 2007, Pub. L. No. 110-85, 121 Stat. 823 (2007) *which did not include a preemption*

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[7] As the New England Journal's editors have now expressly stated, the FDA's current preemptive position is also a threat to the medical profession. *See, e.g.*, Gurfman, G.D., Morrissey, S., Drazen, J.M., *Why Doctors Should Worry About Preemption*, NEJM, Vol. 359:1-3 (July 3, 2008) (editorial by NEJM editors, criticizing FDA position in this case) (available at http://content.nejm.org/cgi/content/full/359/1/1).

provision. The Act instead included a "rule of construction" that the FDA's new authority over labeling did *not* relieve manufacturers of their current responsibilities to provide up-to date safety information and did not affect their ability and responsibility to do so without first securing the FDA's approval; 121 Stat. 925-26; *see* Kessler and Vladeck at 469. As Commissioner Kessler notes, the pharmaceutical industry unsuccessfully sought a preemption provision; when they failed to secure one, opponents of the bill criticized it as "a definite boon to trial lawyers." *Id.* at fn 27. Whether it was a "definite boon" to consumers, their lawyers, pharmaceutical companies, or the State legislatures and courts that have long considered and balanced the interests of these constituencies in the system of tort law, the FDA Amendments Act definitely did *not* authorize preemption.

SUMMARY OF ARGUMENT

The FDA cannot deny that the preamble is not part of the FDA regulation and that it did not go though the formal notice and comment process. Although this Court has sometimes given deference to an agency's interpretive rules—rules that do not have the force of law, but that set forth the agency's understanding of a law which Congress has authorized that agency to interpret via the regulatory process or enforce, *e.g.*, *Auer v. Robbins*, 519 U.S. 452, 461 (1997)—in this case the FDA did not purport to issue an interpretive rule as Congress had not authorized the FDA to preempt or replace state tort law. Instead, the FDA stated its belief on a legal (or political) question, in language resembling a lawyer's

(or lobbyist's) advocacy position. *See* 71 Fed. Reg. 3922, 3934 and 3969 (2006).

However, even if this Court were to view the preamble as an interpretive rule, no deference can be given hereto without fundamentally undermining our system of Federalism for three reasons:

First, the FDA failed to give State authorities any meaningful notice and/or an opportunity to comment and participate in the proceedings as required by Executive Order 13132. The preamble's method of creation instead sought to preempt due process. The FDA's flagrant violation of a **binding** Executive Order designed to safeguard our system of Federalism should not be enabled by this Court.

Second, this procedural violation is exacerbated by the FDA's lack of Congressional authority to determine the preemptive effect of drug labeling rules on state law causes of action. The FDA has simply attempted to seize, in a manner never countenanced by this Court, the States' sovereign authority over their own tort law, in order to assist a special interest. Respect for our system of Federalism requires that this Court reject the Executive branch's effort to impose preemption absent clear Congressional authorization and appropriate respect for procedural norms.

Finally, when an Agency has radically changed its long-standing views, is unable to explain its change in view, and, as here, proceeds in a manner that demonstrates that politics, rather than independent Agency expertise, is the source of the new view, the Agency's arguments for administrative

preemption should be rejected out of respect for our shared system of Federalism. Preemption cannot be allowed to be *implied* based upon political decisions by the Executive Branch acting alone.

ARGUMENT

A. The FDA's Failure to Give The States Proper Notice and an Opportunity to Comment deprives the preamble of any force or entitlement to deference.

The FDA failed to comply with the express, unambiguous, and mandatory directive of Executive Order 13132. No sensible or reasoned excuse is provided by the FDA for its failure to consult with appropriate State officials. The FDA's tautological explanation that it need not consult them, having told States and Local Government in 2000 that the proposed regulations did not preempt state law, because it received no comments from them on Preemption, would make Charles Dodgson blush.[8].

Section 4(d) of Executive Order 13132 *requires* agencies to consult with appropriate State and Local officials whenever an agency foresees the possibility

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[8] Mr. Dodgson, writing as Lewis Carroll, presciently encapsulated the FDA's evident concept of due process in the innovation of his benevolent yet thrifty White Queen, who gave her maid "jam tomorrow and jam yesterday – but never jam today." Lewis Carroll, *The Annotated Alice* 247 (New American Library 1960), as cited in *Aka v. Wash. Hosp. Ctr.*, 156 F.3d 1284, 1301 (D.C. Cir. 1998).

of a conflict between state law and a federally protected interest within the agency's area of regulatory responsibility. Section 4(e) of Executive Order 13132 further specifies that when an agency proposes to act through adjudication or rulemaking to preempt state law, the agency *shall provide* all affected state and local officials with notice and an opportunity to comment and participate in the proceedings.

State Governments have a reasonable basis to rely upon the Executive Order and expect that the Federal Executive Branch would not engage in an end run around due process to avoid what it knew to be unfavorable input and opposition. *See Watters v. Wachovia Bank, N.A.*, – U.S. –, 127 S. Ct. 1559, 1584 (2007) (Stevens, J., Roberts, C.J., and Scalia *dissenting*). When the FDA issued its proposed drug labeling rule in 2000, it stated quite clearly in its notice of rulemaking that "***this proposed rule does not preempt state law.***" 65 Fed. Reg. 81103 (emphasis added). This unequivocal statement was consistent with the FDA's longstanding position on preemption. The FDA therefore expressly told State and local officials that the proposed rule would not preempt or otherwise impact state law, effectively silencing interested parties during the notice and comment period by assuring them that Federalism issues were not at stake.

The process by which the preamble was inserted inappropriately placed expediency above the necessary respect for State governments. *Cf. Community Communications Co., Inc. v. City of Boulder, Colo.*, 455 U.S. 40, 61 (1982) (Rehnquist, J., Burger, C.J.,

and O'Connor, J. dissenting) ("pre-emption, because it involves the supremacy clause, implicates our basic notions of federalism."). In its zeal to assist the peculiar interest of a pressure group, the agency knocked askew the balance of powers and the system of checks and balances—among the branches of our federal government, and between the federal and state governments—that are the structural and functional bedrocks of our system. *Gregory v. Ashcroft*, 501 U.S. 452, 548-9 (1991). Unbalanced and unchecked, the preamble exalts the bureaucratic processes of the executive branch and subordinates the legislative and judicial branches of both the Federal government, and the States themselves, without any Constitutional basis.

Moreover, the preamble ignores the historical roles of the States as sovereigns of their own statutory and common law, in an area in which Congress, deferring to the States, has not legislated: providing compensation for victims of negligence and strict liability in the design and manufacture of pharmaceutical products. Deferring to the preamble's administrative fiat would eradicate, in the guise of preemption, the compensatory and deterrent system, painstakingly built up over more than two centuries of State legislation and jurisprudence, in favor of a void. Preemption in this case is an undefined, unlimited, and an ill-fitting concept, since neither the FDA nor any other federal agency has ever entered, much less fully occupied, the compensatory tort system other than through formal statutory acts of Congress addressing specific medical products, such as with-vaccines, which provide comprehensive systems for

the adjudication of claims and redress of injuries. The preamble does neither. It is nihilism, not preemption.

While the Executive Branch is entitled to assert any position it wishes, it cannot both do so via a legal process which fails to afford State Governments the respect they are due under Federalism, and expect any deference to its views. *See Watters v. Wachovia Bank, N.A.*, 127 S. Ct. 1559, 1582 (2007) (Stevens, J., joined by the Chief Justice and Scalia, J., dissenting). There was certainly no emergency at issue here to justify the hidden process used to create the preamble. As noted above, the FDA's new views on preemption as expressed in amicus briefs had been repeatedly rejected by courts with sufficient time for the FDA to notify State Governments of its intended change in position (so as to comply with Section 4(d) of Executive Order 13132) if it so wished. Failure to do so is an implicit admission of the lack of merit in the FDA's changed position, and self evident unwillingness to have this position exposed to comment and objection by State Governments. This procedural failure is fatal to any application of the preemption language. *Cf. United States v. Mead Corp.*, 533 U.S. 218, 228 (2001)("power to persuade" is related to "thoroughness evident" in agency's consideration of the issue). To rule otherwise would deprive State and Local governments of important historical rights without giving them any voice in the proceedings, while rewarding what was essentially a bait-and-switch by the FDA. The FDA's new views, expressed in the preamble, are therefore entitled to no deference.

B. The FDA Acted Well Outside the Scope of the Authority Delegated to it by Congress and its New Presentation Position is *Ultra Vires*.

In *Riegel v. Medtronic, Inc.*, – U.S. –, 128 S. Ct. 999 (2008) this Court considered the FDA's interpretation of a phrase: "state or local requirements of generally applicability . . .," found in an FDA regulation. *Id.* at 1010. While noting that "substantial deference" could be afforded under *Auer v. Robbins*, 519 U.S. 452, 461 (1997) to the Agency's interpretation of terms in its own regulation, this Court stated that: "[w]e find the agency's explanation less than compelling," and untimely afforded no deference to the FDA's interpretation. *Riegel, id.* at 1011.

While acknowledging this Court's ruling in *Riegel*, the United States argues for *Auer* deference in this case. *United States* Amicus at 26. Yet, the United States failed to acknowledge or discuss the substantial differences between the FDA's action in this case and *Auer* and *Riegel*. These differences are critical in placing the appropriate limits on preemption to protect our system of federalism.

Auer involved regulations promulgated by the Secretary of Labor and published in the CFR establishing a "salary basis" test for overtime to implement the Fair Labor Standards Act. 519 U.S. at 455. These regulations were drafted under what this Court noted was a statutory grant to the Secretary of Labor of "broad authority to 'defin[e] and delimit' the scope of the exemption [in the FLSA] for executive,

administrative, and professional employees." *Id.* at 456.

Because a (1) regulation, (2) was promulgated pursuant to broad statutory authority and (3) "[b]ecause Congress has not 'directly spoken to the precise question at issue,'" *id.* at 457 (*citing Chevron U.S.A., Inc. v. Natural Resources Defense Council, Inc.*, 467 U.S. 837, 842-3 (1984)) this Court gave deference. *Id.* at 461. Yet none of these three prerequisites to *Auer* deference apply here. Unlike in *Auer* and *Riegel*, no regulation promulgated by the FDA is at issue. Likewise, Congress has not granted the FDA authority to address preemption via regulation. To the contrary, Congress recognized the role and primacy of common law, and expressly incorporated a savings clause. *Supra* at 4. Here no regulation is at issue, Congress' stance opposing preemption is unambiguous, and *Auer* deference therefore has no place. *Cf. Christensen v. Harris County*, 529 U.S. 576, 588 (2000) ("*Auer* deference is warranted only when the language of the regulation is ambiguous.").[9]

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[9] The United States' further citation to *Chevron U.S.A., Inc. v. National Resources Defense Counsel, Inc.*, 467 U.S. 837, 842-43 (1984) adds nothing to *Auer*, as the same limits apply. As this Court has noted, "Deference in accordance with Chevron...is warranted only 'when it appears that Congress delegated authority to the agency to make rules carrying the force of law, and that the agency interpretation claiming deference was promulgated in the exercise of that authority.'" *Gonzalez v. Oregon*, 46 U.S. 243, 257 (2006) (quoting *Mead Corp.*, 533 U.S. at 226-27 (*emphasis added*)).

While the United States cites *Geier v. American Honda Motor Corp.*, 529 U.S. 861 (2000) the deference afforded in that case was built on a far different foundation. As this Court discussed at length regarding the NHTSA's airbag and passive seatbelt research and regulation, "the relevant history and background are complex and extensive." *id.* at 883, noting that "DOJ has explained FMUSS 208's objectives, and the interference that 'no airbag' suits pose thereto consistently over time." *Id.* For this reason, the *Geier* majority concluded that "we have no reason to suspect that the Solicitor General's representation of DOT's views reflects anything other than the agency's fair and considered judgment on the matter." *Id.* at 884 (quoting *Auer*, 519 U.S. at 461-462).

In this case there is clearly neither the heavy involvement of Congress in the agency's decision, the extensive rulemaking, nor a consistent Agency position, as found in *Geier*. Rather, the record shows an agency willing to use a last-minute phone call on the eve of a holiday, and refusing to allow anyone to see its handiwork, to attempt a policy sea change by stealth.

The current argument of the Executive Branch presents, in starkest terms, the issue addressed by the dissent in *Watters v. Wachovia Bank, N.A.*, 127 S. Ct. 1559, 1582 (2007): whether *absent a delegation by Congress* to the agency of authority to preempt state laws (delegation the *Watters* opinion found had occurred under the National Bank Act but the FDA does not even claim here) "an administrative agency can assume the power to displace the

duly enacted laws of a state legislature." *Id.* at 1583 (Stevens, J., Roberts, C.J., and Scalia, J., dissenting). If the respect for state authority required by Federalism is to have any meaning *absent clear Congressional authorization* to preempt state laws, the answer must be:

> '[u]nlike Congress, administrative agencies are clearly not designed to represent the interests of States, yet with relative ease they can promulgate comprehensive and detailed regulations that have broad preemption ramifications for state law.' *Id.*, at 908, 120 S. Ct.. 1913 (STEVENS, J., dissenting). For that reason, when an agency purports to decide the scope of federal preemption, a healthy respect for state sovereignty calls for something less than *Chevron* deference. *See* 529 U.S., at 911-912; *see also Medtronic*, 518 U.S., at 512 (O'Connor, J., concurring in part and dissenting in part) ('It is not certain that an agency regulation determining the pre-emptive effect of *any* federal statute is entitled to deference').

Id. at 1584. Addressing the issue presented by the preamble before this court (and assuming, as shown here, no grant by Congress to the agency of authority to preempt) it was appropriately noted in the *Watters* dissent that, absent Congressional authority:

> Nor can the [Agency's] incorporation of that language into a regulation support

> the agency's position: 'Simply put, the existence of a parroting regulation does not change the fact that the question here is not the meaning of the regulation but the meaning of the statute.' *Gonzales v. Oregon*, 546 U.S. 243, 257 (2006). The OCC's argument to the contrary is particularly surprising given that when it promulgated its "same terms and conditions" regulation, it said not one word about preemption or the federalism implications of its rule—an inexplicable elision if a 'fundamental component' of the phrase is the need to operate unfettered by state oversight. Compare 65 Fed. Reg. 12905-12910 (2000), with Exec. Order No. 13132, §§ 2, 4, 64 Fed. Reg. 43255, 43257 (1999) (requiring agencies to explicitly consider the 'federalism implications' of their chosen policies and to hesitate before preempting state laws.

Id. at 1584-5.

Here, Congress has not provided the FDA any express or implied authority to determine the preemptive scope of its regulations on state law causes of action. The United States does not even try to claim any such clear and unambiguous delegation. This should be the end of the matter. As this Court noted in creating a "plain statement rule," preemption must come from *Congress* and "Congress should make its intention 'clear and manifest' if it intends to

preempt the historic powers of the states." *Gregory v. Ashcroft*, 501 U.S. at 461.

This Court's holding in *Adams Fruit Co. v. Barrett*, 494 U.S. 638, 650 (1990), declining to give deference to the Secretary of Labor's view on the scope of civil remedies available to redress violations of regulations, also calls for non-deference. In *Adams Fruit*, this Court warned that, although agency determinations within the scope of delegated authority are entitled to deference, it is fundamental "that an agency may not bootstrap itself into an area in which it has no jurisdiction." *Id.* Likewise, an agency ruling that broadens its own jurisdiction should be carefully scrutinized. *See, e.g., Hi-Craft Clothing v. NLRB*, 660 F.2d 910, 916 (3d Cir. 1981). Courts should be skeptical of the FDA's assertion of power, as it is highly unlikely that Congress would implicitly delegate to the agency the power to define the scope of its own power. *See Ass'n of American Physicians & Surgeons v. United States Food & Drug Admin.*, 226 F. Supp. 2d 204, 212 (D.D.C. 2002) (finding that the FDA exceeded its authority in adopting regulations requiring drug manufacturers to conduct certain testing on pediatric populations).

Here, Congress has never delegated to the FDA authority to determine the preemptive effect of drug labeling rules on state law causes of action. To the contrary, as noted above at 4, Congress specifically declined to provide a federal damages remedy in the FDCA because state law damages remedies were available and subsequently added a savings clause. Having made no effort to legislate on the topic of

drug-related damages remedies, and then adding a savings clause to preserve the remedies provided by State law, Congress can hardly be said to have authorized the FDA to supersede the damages remedies traditionally provided by the states, let alone to have made a "plain statement" of intent to preempt. *See Gregory v. Ashcroft*, 501 U.S. at 460-61.

The preamble does not merely preempt or preclude the development or enactment of some yet-inchoate State law. What we know as "the common law" is both vast and specific, woven over decades into a rich tapestry, interpreting and elaborating on State statute, and in turn being hemmed and bordered by it. As Justice Holmes observed famously, "the common law is not a brooding omnipresence in the sky but the articulate voice of some sovereign or quasi-sovereign that can be identified . . . it is always the law of some State . . ." *Southern Pacific v. Jensen*, 24 U.S. 205, 222 (1917) (dissent); cited, *inter alia*, in *American Dredging Co. v. Miller*, 510 U.S. 443, 459 (1994) and *Salve Regina College v. Russell*, 499 U.S. 225, 238 (1991).

These principles, combined with Congress' express rejection of a proposal to include a federal private right of action in the FDCA because "a common law right of action already exists," and the absence of any provision within the FDCA delegating to the FDA authority to determine the preemptive effect of drug labeling rules on state law causes of action, leads to one conclusion—Congress could not have, and did not, confer upon the FDA the power to legislate for itself and unilaterally determine whether its

drug labeling regulations preempt state law. Therefore, the FDA's proposed preemption analysis is nothing more than an *ultra vires* political statement which exceeds the scope of the FDA's congressional authority and, as such, is due no deference from this Court.

C. The Preamble's Reversal of the FDA's Longstanding Position Against Preemption Undermines the Argument for Deference.

Assuming that the FDA had the requisite congressional authority to determine the preemptive scope of its regulations—which it plainly did not—deference is nevertheless unwarranted because the preamble reverses the FDA's longstanding position against preemption. As has been noted by several courts: "FDA's current view of the preemptive effect of its labeling regulations is a 180-degree reversal of its prior position." *In re Bextra and Celebrex Mktg. Sales Practices & Prod. Liab. Litig.*, No. M:05-169 CRB, 2006 WL 2374742 at 18 (N.D. Cal. Aug. 16, 2006). This has caused courts, in reasoned opinions, to reject the preamble and the FDA's claims of preemption. *See, e.g.*, *In re Vioxx Prod. Liab. Lit.*, 501 F.Supp 2d 776 (E.D. La. 2007) (noting change in prior position and refusing to give the preamble *Auer* or *Chevron* deference).

This Court has repeatedly held that an agency assertion of preemption that reverses prior longstanding agency policy is entitled to little or no weight by the courts. *See Bates v. Dow Agrosciences, L.L.C.*, 544 U.S. 431, 449 (2005). In *Bates*, this Court

ruled that FIFRA, a federal statute governing the safety of pesticides, did not preempt state common law tort claims. In doing so, this Court rejected arguments made by the government in *amicus* briefs, and in fact chastised the EPA for engaging in the exact same policy flip-flop at issue herein: "The notion that FIFRA contains a nonambiguous command to pre-empt the types of tort claims that parallel FIFRA's misbranding requirements is particularly dubious given that just five years ago the United States advocated the [opposite interpretation]." *Id.*

As in *Bates*, this Court should greet skeptically any suggestion that the FDA's drug labeling requirements preempt state law, given that the FDA itself advocated the opposite interpretation just six years ago. The similarities between the nature and timing of the EPA's conduct in *Bates* and the FDA's conduct herein demand careful consideration of the strict adherence to the "canons of interpretation" favoring principles of *stare decisis* over the more volatile political opinions within federal agencies. *Bates*, 544 U.S. at 449.

As set forth above, the FDA's abrupt change in position regarding the preemptive scope of its drug labeling requirements reverses an anti-preemption policy which spanned decades, including an express statement by the FDA in 2000 that: "this proposal does not preempt state law." 65 Fed. Reg. 81082, 81103 (2000). During this time, numerous courts throughout the country relied on the FDA's interpretation of its regulations while continuing the grand and endless project of developing and refining a sub-

stantial body of state common law,[10] and for rejecting the very same preemption arguments made herein. Importantly, the final rule does not amend any of the regulations upon which these courts have relied in finding no preemption. Accordingly, the FDA's abrupt change in position unnecessarily disrupts not only its own longstanding principles, but principles of *stare decisis* as well.

Ultimately, the FDA's preamble is simply an unwarranted and arbitrary change in position without any concomitant change in the law. For these reasons, the Court should give no deference.

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[10] As California Chief Justice Roger Traynor observed of the common law process, "The law was not built in a day, and with luck it will never be finished." Traynor, "*La Rude Vita, La Dolce Giustizia; or Hard Cases Can Make Good Law*," 29 U. Chi. L. Rev. 223, 236 (1962). It would be unlucky indeed for our system of Federalism were an administrative agency to finish off the common law of tort with a "preamble."

CONCLUSION

For the preceding reasons, the judgment of the Supreme Court of Vermont should be affirmed.

Respectfully submitted,

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No. 06-1249

In the Supreme Court of the United States

WYETH,

Petitioner,

v.

DIANA LEVINE

Respondent.

On Writ of Certiorari to the Supreme Court of Vermont

AFFIDAVIT OF SUSAN PARNAS FREDERICK

AFFIDAVIT

I, Susan Parnas Frederick, do hereby testify as follows under penalty of perjury.

I am the Federal Affairs Counsel for the National Conference of State Legislatures. I am a member of the bar of the Commonwealth of Virginia. In my responsibility as Federal Affairs Counsel for the National Conference of State Legislatures, I am responsible for acting as the liaison to the Executive Branch for State legislatures regarding Executive Order 13132 ("Federalism").

On December 2, 2000, the Food and Drug Administration submitted a Notice of Proposed Rule Making ("NPRM") regarding prescription drug labeling. *See Federal Register*, Volume 65, Number 241, p. 81103, December 22, 2000. Because the NPRM expressly stated that there would be no Federalism implications in the regulation, and because the proposed rule stated that it would not preempt state laws, the National Conference of State Legislatures did not submit comments. Because the Regulation expressly stated that there would be no preemption, the formal consultation requirements of Executive Order 13132 were not triggered.

At the end of the day on December 30, 2005, I received a call in my office from FDA intergovernmental staff. This staffer told me that the FDA planned to finalize its long-dormant labeling rule in early January 2006 and would be including a statement that the provisions of the Prescription Drug Labeling Rule would preempt state product liability laws. I immediately asked to be placed in touch with FDA's general counsel's office, asked for a copy of the pro-

posed "policy statement," for the consultation process under Executive Order 13132 to occur, and for the Notice and comment period to be re-opened. Upon receiving a call from general counsel's office for the FDA, I was informed by Mr. Randy Luttig that NCSL could not review this proposed language in advance of its publication, that this telephone call constituted the consultation under Executive Order 13132, and that the comment period was closed and would not be reopened to permit NCSL to submit comments on the new language.

In a follow-up conversation with FDA staff, I was informed that the FDA considers the requirement of Executive Order 13132 satisfied, and was again told I would not be able to review a copy of the proposed "policy statement," I subsequently learned that FDA had received and accepted numerous late, non-public, comments from industry on the proposed regulation.

Because the FDA had refused to follow the process required by Executive Order 13132, which requires that meaningful consultation with state officials or their national associations is to occur *prior* to any notice of proposed rule making being published in the Federal Register our organization wrote to Secretary Leavitt to complain about the FDA's conduct. *See* http://www.ncls.org/programs/press/2006/060113leavitt.htm.

The foregoing is true and correct, and if called to I could testify competently thereto.

Dated: August 14, 2008.

Susan Parnas Frederick

Susan Parnas Frederick

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In The
Supreme Court of the United States

WYETH,

Petitioner,

v.

DIANA LEVINE,

Respondent.

On Writ Of Certiorari
To The Supreme Court Of Vermont

BRIEF OF *NEW ENGLAND JOURNAL OF MEDICINE* EDITORS AND AUTHORS AS *AMICI CURIAE* IN SUPPORT OF RESPONDENT

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INTEREST OF *AMICI CURIAE*

Amici curiae, all of whom hold degrees in medicine and related fields, are ten current and former editors and contributing authors of the New England Journal of Medicine ("NEJM"), including each editor-in-chief of NEJM since 1977.[1] NEJM is the oldest continuously published medical journal in the world, and has published numerous scholarly articles on, among other things, advances in drug therapy, prescription drug side effects, and the role of the United States Food and Drug Administration ("FDA") and the pharmaceutical industry in our health care system. For nearly 200 years, physicians have turned to NEJM as a source of important new information to guide their medical practice.

Beginning in the year 2000, *amici* **Jeffrey M. Drazen, M.D.**, and **Gregory D. Curfman, M.D.**, have served as NEJM's Editor-in-Chief and Executive Editor, respectively. Beginning in 2002, *amicus* **Stephen Morrissey, Ph.D.**, has served as Managing Editor of NEJM. Together, Drs. Drazen, Curfman, and Morrissey have more than 50 years of experience as editors.

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[1] Pursuant to Rule 37.6, *amici* state that no counsel for a party authored any part of this brief, and no person or entity, other than *amici* and their counsel, made any monetary contribution to the preparation or submission of this brief. Counsel of record for both parties have consented to the filing of this brief.

Amicus **Marcia Angell** served as NEJM's Executive Editor between 1988 and 1999 and as its Editor-in-Chief between 1999 and 2000. *Amicus* **Jerome P. Kassirer, M.D.**, currently Distinguished Professor at Tufts University School of Medicine, served as NEJM's Editor-in-Chief between 1991 and 1999, after which he was named Editor-in-Chief Emeritus. Between 1977 and 1991, *amicus* **Arnold S. Relman, M.D.**, served as NEJM's Editor-in-Chief, after which he became Editor-in-Chief Emeritus.

Amicus **Paul D. Stolley, M.D., M.P.H.**, former Professor and Chairman of the University of Maryland's Department of Epidemiology and Preventive Medicine and for five years a member of the FDA's Biometrics and Epidemiology Advisory Committee, served on NEJM's editorial board from 1989-1993, and has written 15 articles published in NEJM. *Amicus* **Harlan M. Krumholz, M.D., S.M.**, the Harold H. Hines, Jr. Professor of Medicine and Epidemiology and Public Health at Yale University School of Medicine and Editor-in-Chief of *Circulation: Cardiovascular Quality and Outcomes*, has authored 15 articles published in NEJM. *Amicus* **Stuart Rich, M.D.**, Professor of Medicine at the University of Chicago, has written six articles published in NEJM, including a study on the relationship between Pondimin/Redux and primary pulmonary hypertension. Finally, *amicus* **Eric J. Topol, M.D.**, the Founding Dean of the Scripps School of Medicine and Professor of Translational Genomics at The Scripps Research Institute, has written 35 articles published in NEJM.

The issue before this Court is one of immense importance from the perspective of public health and safety. *Amici*'s professional responsibilities have included evaluating the efficacy of prescription pharmaceutical drugs, the conduct of the pharmaceutical industry, and the ability of the FDA to ensure that safe and effective medications with adequate warnings are made available to American consumers and, when necessary, withdrawn from the marketplace. The matter under review by this Court – namely, whether federal law preempts failure-to-warn claims relating to prescription drugs – falls directly within *amici*'s professional responsibility to ensure that prescription drugs best serve the public's health. It is in performing that role that *amici* feel compelled to ask this Court to affirm the decision of the court below.

SUMMARY OF ARGUMENT

The argument of Petitioner and its *amici* ("Petitioner/*Amici*") that federal preemption of state law failure-to-warn claims involving prescription drugs will actually make the world a safer place is riddled with factual fallacies. First, contrary to Petitioner's/*Amici*'s necessary premise, the FDA is in no position to ensure the safety of prescription drugs. Not only is the FDA seriously hampered in its ability to determine the risks of drugs before they are

approved for sale, but it has proven inadequate to the task of addressing hazards that only become apparent after a drug has been widely marketed to an unsuspecting public. Post-approval dangers posed by drugs placed into the market are unfortunately quite common. However, the FDA's ability to either anticipate these risks or react expeditiously once they have been revealed has been limited by serious information-gathering constraints in both pre- and post-approval settings.

Much of this stems from the fact that the FDA is heavily dependent on the drug makers themselves for the information on which the agency bases its decisions. Not surprisingly, this dependence has its drawbacks. Pharmaceutical companies at times learn about dangers caused by their drugs long before the FDA does, but have failed to disclose this information to the FDA. Thus, as exemplified by the cases of Pondimin/Redux, Vioxx, and Trasylol, the drug companies have withheld key information from the FDA and ardently negotiated against stricter label warnings – all the while continuing to market their unsafe drugs to an unsuspecting public. In the case of these three drugs alone, literally tens of thousands of American lives have been lost or ruined long after the manufacturers realized that the drugs were not safe.

In light of this sad reality, Petitioner's/*Amici*'s argument that failure-to-warn suits actually pose a danger to public health is nothing short of specious.

The theory that the risk of tort liability causes drug manufacturers to "over-warn" of the dangers of their drugs (thereby scaring patients away from drugs they need) not only has no empirical support, but it ignores the fact that *under*-warning has, unmistakably and tragically, exacted a terrible toll on public health and safety.

Equally specious are Petitioner's/*Amici*'s arguments that the $700 *billion* pharmaceutical industry, which grows more robust with every passing year, is somehow economically stifled by the products liability system. In arguing that immunity from failure-to-warn suits should uniquely be provided to their industry, they fail to consider that the tort system has played a crucial role in assisting the FDA in evaluating the benefits and risks of prescription drugs. As the examples of Pondimin/Redux, Vioxx, and Trasylol potently demonstrate, the FDA alone simply lacks the ability to serve as the sole guarantor of drug safety. Without the tort system, the FDA would be stripped of an essential source of information that the agency has consistently relied on when making its regulatory decisions, and the American public would be deprived of a vital deterrent against pharmaceutical company misconduct. Thus, rather than promote public health, the preemption of failure-to-warn claims would substantially *threaten* it. *Amici* therefore urge this Court to reject Petitioner's request for preemption.

ARGUMENT

I. THE FDA LACKS SUFFICIENT INFORMATION AND RESOURCES TO SERVE AS THE SOLE MONITOR OF PHARMACEUTICAL RISKS

The position of Petitioner/*Amici* is that any product label approved by the FDA must necessarily constitute both the minimum and maximum that should be required. Their premise is that the FDA's function will be disrupted if it is not left alone to strike the proper balance between safety and efficacy. Product liability lawsuits, they argue, prevent the FDA from fulfilling its mission of ensuring that consumers receive optimal warning of the dangers of prescription drugs.

But for the FDA to strike that proper balance, it must be privy to all pertinent information regarding the benefits and risks of all prescription drugs. The FDA neither has nor could have the resources to perform this Herculean function, given the 11,000 FDA-regulated drugs on the market and the nearly one hundred more approved each year.[2] In fact, three

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[2] *See* FDA Center for Drug Evaluation and Research, U.S. Dep't of Health and Human Servs. 2005 Report to the Nation: Improving Public Health Through Human Drugs 12 <http://www.fda.gov/cder/reports/rtn/2005/rtn2005.pdf>; FDA Science Board Report, *FDA Science and Mission at Risk* (2007) <http://www.fda.gov/ohrms/dockets/AC/07/briefing/2007-4329b_02_01_FDA%20Report%20on%20Science%20and%20Technology.pdf> ("FDA 2007").

recent analyses of the FDA's drug safety oversight – two by the Government Accountability Office ("GAO") and the other by the congressionally chartered National Academy of Science's Institute of Medicine ("IOM") – criticized the FDA's ability to keep unsafe drugs off the market and to respond effectively to observed hazards.[3] Many of these difficulties, however, are endemic to the FDA's system of acquiring information.

The FDA receives pre-market information regarding Adverse Drug Reactions ("ADRs") from clinical trials that are conducted by the drug companies themselves. While clinical trials represent an important aspect of drug development by providing efficacy assessments, their ability to assess a complete safety profile is inherently limited. *IOM Report* at 38. To demonstrate efficacy, studies generally range between a few hundred to 3000 subjects with a duration of from six to eight weeks to two years. These studies cannot fully account for: 1) the effects of long-term cumulative dose or latent ADRs; 2) rare ADRs or those most pronounced in sub-populations; or 3) potential ADRs not accounted for in clinical trial

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[3] *See* U.S. Gov't Accountability Office, *Drug Safety: Improvement Needed in FDA's Post-market Decision-making and Oversight Process* <www.gao.gov/cgi-bin/getrpt?GAO-06-402> ("GAO 2006"); U.S. Gov't Accountability Office, *Drug Safety: FDA's Oversight of the Promotion of Drugs for Off-Label Uses* <http://www.gao.gov/new.items/d08835.pdf>; Institute of Med. of the National Academy of Science, *The Future of Drug Safety* (Baciu, Alina, *et al.*, eds., 2006) ("*IOM Report*").

designs. In addition, for ethical reasons studies are often conducted on "lower-risk" rather than "higher-risk" populations.

Given that the FDA conducts no independent testing, the information it relies on is necessarily provided by the party most interested in bringing the drug to market – the drug manufacturer. Even under the best of circumstances, the FDA often lacks the ability of those conducting a study to interpret the data generated. FDA 2007 at 31. Moreover, the FDA's own Science Board found that the FDA lacks sufficient expertise in quantitative methods, such as statistics and biomathematics, to effectively assess products and guide sponsors to design valid and informative studies. *Id.* at 35. As a result of these weaknesses, manufacturers, rather than the FDA, are often the first to learn of serious ADRs related to their drugs, while the FDA is wholly reliant upon their reporting. The system's limitations have been confirmed by one early analysis by the GAO, which concluded that 51.5 percent of all approved drugs had at least one serious ADR not recognized before approval.[4]

Post-approval evaluation of drug risks has not cured the serious defects in the pre-approval process. Although the FDA generally requires companies

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[4] U.S. Gov't Accountability Office, *Drug Safety: Post-Approval Risks 1975-1986* at 3 <http://archive.gao.gov/d24t8/141456.pdf>.

marketing new drugs to perform post-approval or "Phase IV" studies,[5] these studies until very recently have been almost completely out of the FDA's control.[6] Historically, the FDA has lacked the authority to require such studies, GAO 2006 at 5, to grant conditional approval for drugs requiring further study, or to conduct direct legal action in this regard. Indeed, FDA action against a drug company for failing to submit clinical study information virtually never occurs. Given this lack of regulatory consequences, in 2003, the estimated post-market study completion rate was only 24 percent. GAO 2006 at 28. An FDA report that checked unsatisfied commitments as of September 2005 found that of 1,231, almost two-thirds (797) were "pending," *i.e.* not even initiated, with just 21 percent listed as "ongoing" or "delayed."

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[5] Tufts Ctr. for the Study of Drug Dev., "FDA Requested Post-marketing Studies in 73% of Recent New Drug Approvals," *Impact Report*, July-Aug. 2004, <http://csdd.tufts.edu/_documents/www/Doc_309_42_893.pdf>.

[6] The FDA Amendments Act of 2007 tries to address this problem by giving the agency authority to require Phase IV studies for "serious risk[s]" and to set timetables for study completion. FDAAA, tit. IX, sec. 901(a), § 505(o)(3)(B-E), 121 Stat. 823, 923-924. As explained in the *amicus curiae brief* of AARP, these amendments will only have a very limited ability to enhance the FDA's goal of addressing post-approval risks.

Many of the so-called "pending" study commitments even lacked a completion deadline.[7]

The FDA also attempts to monitor post-approval performance by gathering reports of ADRs through its Adverse Event Reporting System and "MedWatch" program. 21 C.F.R. § 310.305 (2006). While this is indeed a critical system for data-gathering, by the FDA's own estimate "it hears of less than 1 percent of serious adverse reactions."[8] Even to the extent information is received, drug companies are often in a better position to distinguish between drug-induced and naturally occurring events. Just receiving ADRs at times can be of limited utility, because the FDA often will not know how many people use a given drug in order to calculate the incidence of any adverse reaction.[9] These weaknesses contribute to the FDA's difficulty in promptly identifying serious, less common, ADRs, making it even more dependent on

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[7] *See* Report on the Performance of Drug and Biologics Firms in Conducting Post-Marketing Commitment Studies, 71 Fed. Reg. 10978-79 (2006).

[8] Reauthorization of the PDUFA: Hearing Before the Subcommittee on Health of the H. Comm. on Energy and Commerce, 107th Cong. 49 (2002) (statement of Rep. Henry A. Waxman) <http://energycommerce.house.gov/reparchives/107/action/107-93.pdf>; *See* also *IOM Report* at 53 (reporting that the 400,000 reports received each year represent only a "small fraction of all adverse effects of drugs.").

[9] *See* Steenburg, "*The Food and Drug Administration's Use of Post-Marketing (Phase IV) Study Requirements: Exception to the Rule?*" 61 Food & Drug L.J. 295, 298, n.30. (2006).

pharmaceutical companies to share complete information.

II. THE FDA'S LIMITATIONS AS THE SOLE MONITOR OF PHARMACEUTICAL RISKS ARE ILLUSTRATED BY DRUGS THAT HAD TO BE WITHDRAWN FOR SAFETY REASONS

There can be little argument regarding the risk/benefit calculus for drugs withdrawn due to safety concerns – by definition their initial warnings proved inadequate. As shown in Appendix "A," drugs requiring complete withdrawal from the market for safety reasons are not rare.[10] While drug withdrawals are the ultimate protection for public safety, withdrawals are also the most extreme remedy that can be taken by the FDA. Withdrawal is often the result of an assessment that can take years to develop, as is demonstrated by the length of time between approval and withdrawal for many of the drugs listed in Appendix "A." The FDA has many options before complete withdrawal. For one, heightened warnings, including "black box" warnings, can be given for a

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[10] *See, e.g.*, Wysocki, *et al.*, "*Adverse Drug Event Surveillance and Drug Withdrawals in the United States, 1969-2002,*" 165 Arch. Int. Med. 1363 (2005); 21 C.F.R. § 215; "List of Drug Products that have been Withdrawn or Removed from the Market for Reasons of Safety or Effectiveness" <http://www.fda.gov/ohrms/dockets/98fr/100898b.txt>; FDA CDER, Report to the Nation: 2005 <http://www.fda.gov/CDER/reports/rtn/2005/rtn2005-4.htm>.

drug. A pharmaceutical company may even unilaterally add new warnings to their drugs, subject to subsequent FDA approval. *See Osburn v. Anchor Labs., Inc.*, 825 F.2d 908, 913 (5th Cir. 1987) (discussing 21 C.F.R. § 314.70).[11]

Often, withdrawals occur only after lengthy negotiations between the FDA and manufacturers over appropriate warnings. Indeed, although the majority of drug withdrawals eventually occur worldwide, the FDA as a result has at times been comparatively slow to act. (*See, e.g.,* trovafloxacin, suspended in Europe in 1997, but not until 2000 in the U.S., and troglitazone ("Trovan"), withdrawn from the U.K. in 1997, but not suspended until 2000 in the U.S.). This delay can be compounded when manufacturers actively withhold critical information from the FDA in order to delay the implementation or severity of warnings, as was the case with Redux/Pondimin, Vioxx, and Trasylol, discussed below.

In the examples of Redux/Pondimin and Vioxx, discovery conducted during the course of product liability litigation has revealed that the pharmaceutical companies were aware of serious ADRs long before the FDA, but that they failed to provide information to the FDA even while patients were being

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[11] While Petitioner/*Amici* might argue that 21 C.F.R. § 314.70 is limited to "new" evidence, such a reading would not comport with the scientific process. Scientific information is acquired over time with "older" information informing "new" information until a new conclusion is drawn.

injured.[12] As a result, tens of thousands of patients were unnecessarily exposed to potentially life-threatening conditions. These examples demonstrate that the FDA, heavily reliant upon industry-supplied data, cannot reasonably be expected to be the sole guarantor of the nation's drug safety.[13]

A. Fenfluramine/Dexfenfluramine (Pondimin/ Redux)

Fenfluramine, marketed as Pondimin by American Home Products ("AHP," currently known as "Wyeth"), was an anti-obesity drug that was approved by the FDA in 1973 for short-term use. Dexfenfluramine, containing one of Pondimin's two molecules, was marketed by AHP beginning in June 1996 as "Redux." In September 1997, years after its risks became known, both drugs were finally withdrawn from the market because they were linked to two very serious conditions: valvular heart disease and primary pulmonary hypertension ("PPH"). *See* 64 Fed. Reg. 10944-01 (1999), 21 C.F.R. § 216.24 (1999).

PPH is a rare, disabling, and usually fatal disease that occurs in the general population at the rate

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[12] *See* Curtin, Draven & Morrissey, *et al.*, *"Preamble Preemption and the Challenged Role of Failure to Warn and Defective Design Pharmaceutical Cases in Revealing Scientific Fraud, Marketing Mischief, and Conflicts of Interest,"* 35 Hofstra Law Rev. 1773 at 1782-83 (2007) (listing examples).

[13] *See* Curfman, *et al.*, *"Why Doctors Should Worry about Preemption,"* NEJM, 359:1 (2008).

of only one or two per million. Fenfluramine's link to PPH was referenced in the scientific literature as early as the 1970's[14] and was certainly known to occur by 1981.[15] Moreover, in December 1993, French pulmonologist Francois Brenot published an article, entitled "Primary Pulmonary Hypertension and Fenfluramine Use," that surveyed fenfluramine-related PPH prior "case reports" in the medical literature. Plotting 73 cases observed and confirmed in various European clinics, Brenot found that fifteen patients, or twenty percent, had ingested fenfluramine.[16]

However, ADRs for fenfluramine-related PPH prior to 1992 were rare, because sales of Pondimin were not significant. This began to change in 1992 when a series of articles related to an AHP-supported study by Dr. Michael Weintraub appeared in the Journal of Clinical Pharmacology and Therapy. These advocated the use of fenfluramine in combination with the generic drug phentermine to achieve weight loss without the adverse effects of fenfluramine

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[14] *See* Buczko, *"Effect of Fenfluramine on 5-Hydroxytryptamin Uptake and Release,"* British J. Pharmacol., 53(4): 633-38 (1975); Seiler, *et al., "On the Role of Serotonin and the Pathogenesis of Pulmonary Hypertension,"* Clinical Experimental Pharmacology, Physiology, 3(4): 323-30 (1976).

[15] Douglas, *et al., "Pulmonary Hypertension and Fenfluramine,"* 6296 Brit. Med. J. 881-83 (1981).

[16] Brenot, *et al., "Primary Pulmonary Hypertension and Fenfluramine Use,"* Br. Heart J., Vol. 70(6) 537-541 (Dec. 1993).

mono-therapy. This regimen popularly became known as "Fen-Phen." Between 1993 and 1997, sales of Pondimin, the "fen" in fen-phen, rose exponentially.[17]

Between late 1994 and early 1995, AHP acquired American Cyanamid and the rights to bring dexfenfluramine (Redux) to market. Predictions indicated that Redux would create sales of $1 billion in its first three years on the market, depending upon whether or not there would have to be significant warnings about PPH. With so much at stake in gaining Redux's approval by the FDA, AHP chose not to inform the FDA that it was aware of ten times more Pondimin-related PPH cases than were listed on the Pondimin product label.[18]

Virtually any scientific doubt regarding PPH causation ended in March 1995 upon presentation of the interim results of an epidemiologic study sponsored by Servier, AHP's recently acquired partner in the distribution of dexfenfluramine. This study linked fenfluramine to PPH, showing that diagnosis was

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[17] Salbu, "*Off-Label Use, Prescription, and Marketing of FDA-Approved Drugs: An Assessment of Legislative and Regulatory Policy*," 51 FLLR 181, 203 (April 1999).

[18] Avorn, *Powerful Medicines*, New York: Random House (2004) at 74-75.

nine times more likely in those exposed at all to the drug.[19]

Nevertheless, AHP's package insert and Physician's Desk Reference entry for Pondimin between January 1989 and December 1996 continued to mention just four reported cases of PPH in which only one person died. Moreover, this was the only Pondimin "warning" regarding PPH that AHP provided to the medical community or American public between 1989 and late 1996. The "warning" section of the Pondimin product label itself was silent about PPH.

Instead of sending out a "Dear Doctor" letter or moving to change its warnings in response to the study and ADRs it was accumulating on PPH, AHP spent its resources fighting the requirement that it include a "black box" warning regarding PPH on its

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[19] The "IPPHS" study was a prospective case-controlled human epidemiological study conducted in 35 centers in Europe. Abenhaim, *et al.*, *"Appetite Suppressant Drugs and the Risk of Primary Pulmonary Hypertension,"* 335 NEJM 609-16 (Aug. 29, 1996). Ninety-five patients with pulmonary hypertension were compared with 355 control subjects. When appetite suppressants were used for greater than three months, the study demonstrated a 23-fold increased risk of developing pulmonary hypertension. The authors concluded that the evidence indicated that appetite suppressants caused pulmonary hypertension. *See also* Rich, *et al.*, *"Anorexigens and Pulmonary Hypertension in the United States: Results from the Surveillance of North American Pulmonary Hypertension,"* 117 CHEST 871 (Mar. 2000).

packaging[20] – even though internally AHP circulated a "death listing report" to keep track of the number of Pondimin consumers dying from PPH.[21] Nevertheless, it was not until July 1996, that a draft label revision was finally submitted to the FDA, and January 1997 that AHP's first "Dear Health Care Professional" letter was sent to American physicians.

In July 1997, AHP disclosed to the FDA that a cluster of fen-phen related valvular heart disease cases had been reported and analyzed by the Mayo Clinic in March 1997. These cases revealed valvular heart disease in patients taking fen-phen.[22] It was subsequently learned that AHP had been receiving dozens of reports of heart valvulopathy since the

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[20] *See In Re: DIET DRUGS (Phentermine, Fenfluramine, Dexfenfluramine) Products Liability Litigation*, 2003 WL 22023361 at 8 (E.D.Pa. 2003) (Exhibit P-78: November 22, 1995 Memo re: Dexfenfluramine Assessment states on bates stamped page AHP-Q-00013941: "[e]very attempt will be made to ensure that no 'Black Box' Warnings, restrictions of use or negative statements find their way into the Redux labeling.") Shortly thereafter, Wyeth V.P. JoAlene Dolan was able to write: "The meeting with FDA yesterday was a tremendous success! No black box." Mundy, Dispensing with the Truth, New York: St. Martin's Griffin (2001) at 52.

[21] Mundy, "Pillow-boxed In," *Washington Monthly*, Oct. 2003 <http://findarticles.com/p/articles/mi_m1316/is_10_35/ai_n27677094>.

[22] Connolly, *et al.*, "*Valvular Heart Disease Associated with Fenfluramine-Phentermine*," 337 NEJM 581-88 (1997). (Twenty-four women who had used fenfluramine (some for less than three months) had developed heart valve disease diagnosed by echocardiogram.)

early 1990's though they were never reported to the FDA.[23]

While AHP was receiving this dire news regarding the adverse health impacts of Redux and Pondimin, both drugs were proving to be economic blockbusters. In 1996 alone, one million people used Redux while six million used Pondimin. Also in 1996, over eighteen million prescriptions for fen-phen were filled in the United States.[24] Tragically, this marketing success was directly proportional to the grave health consequences of AHP's diet drugs. If one assumes the accuracy of IPPHS's conclusion that "the absolute risk is estimated to be 100 cases of PPH per million users," then in 1996 alone, 700 people contracted generally fatal PPH in exchange for at best minor, temporary weight loss.

B. Rofecoxib (Vioxx)

Rofecoxib, marketed under the name Vioxx, was one of a new breed of nonsteroidal anti-inflammatory drugs (NSAIDs) – COX-2 inhibitors – that were designed to compete with the extremely profitable and growing market of nonselective anti-inflammatory

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[23] *See In Re: Diet Drugs (Phentermine/Fenfluramine/ Dexfenfluramine) Products Liability Litigation*, 369 F.3d 293 (3rd Cir. 2004).

[24] McGrath, *"Only a Matter of Time: Lessons Unlearned at the Food And Drug Administration Keep Americans at Risk,"* Food and Drug Law Journal, 60 Food DLJ 603, 616 (2005); Salbu, *supra*, at 203.

drugs, such as Naproxen (Aleve) and Ibuprofen. Once approved by the FDA on May 19, 1999, Vioxx quickly became one of the most successful drugs in pharmaceutical history, averaging over two billion dollars in sales per year,[25] with total sales from 1999 through 2004 exceeding ten *billion* dollars. But just five years after its introduction, on September 30, 2004, Vioxx was withdrawn from the market due to cardiovascular problems resulting in heart attacks, strokes, and death.

The likelihood that Vioxx would cause cardiovascular problems was known to Merck not only well before 2004 but also before its 1999 release date. In 1997, a clinical trial revealed that Vioxx resulted in systemic reduction of a critical component to the human body's defense mechanism against heart attacks, prostacyclin.[26] Nevertheless, before Vioxx was released, Merck failed to test the potential for Vioxx to cause cardiovascular problems.[27]

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[25] Johnson, "Merck Agrees to Blanket Settlement on Vioxx," Washington Post, Nov. 10, 2007 <http://www.washingtonpost.com/wp-dyn/content/article/2007/11/09/ARZ00711.html

[26] *See* Catella-Larson, *et al.*, "Selective Inhibition of Cyclooxygenase II in the Elderly: Effects on Sodium Balance, Hemodynamics, and Vasoactive Eicosanoids" <http://www.vioxxdocuments.com/Documents/Krumholz_Vioxx/Morrison1998.pdf>.

[27] *See* Psaty, *et al.*, *"COX-2 Inhibitors – Lessons in Drug Safety,"* 352 NEJM 1133, 1134 (2005).

Thus, when Vioxx was first approved for sale in 1999, its label contained no meaningful warning describing a risk of adverse cardiovascular events, such as heart attacks and strokes.[28] Nor was there a Phase-IV plan in place for Merck to conduct a study assessing these risks. Instead, Merck chose to conduct an 8,000 patient trial, called "VIGOR," with the hope of furthering Vioxx's sales at the expense of competing Naproxen. Merck hoped that the trial would aid sales by demonstrating that Vioxx resulted in fewer gastrointestinal problems than Naproxen, these being a known side-effect of most NSAIDs. Instead, early results of the study showed that patients taking Vioxx experienced four times the number of heart attacks (the final results revised this to five times the number of heart attacks) than patients taking Naproxen. In an internal memo dated March 9, 2000, Merck Research Laboratories' President Dr. Edward Scolnick, wrote: "The CV [cardiovascular] events are clearly there . . . [T]his is real . . . " *McDarby*, *supra* at 14.

Eighteen days after receiving these results linking Vioxx to heart attacks, Merck issued a press release attributing the difference in the incidence of heart attacks in the VIGOR study to an alleged

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[28] Merck & Co., Inc., Vioxx (Rofecoxib Tablets and Oral Suspension) label, NDA 21-042 <http://www.fda.gov/cder/foi/nda/99/021042_52_vioxx_prntlbl.pdf>.

cardio-protective effect of naproxen.[29] Merck put forward this theory despite being told by its own expert consultants that they had no clinical evidence that naproxen was cardio-protective. *McDarby, supra* at 30. Nevertheless, this naproxen explanation was disseminated to the public and the medical community through numerous press releases, direct mailings to physicians, and Merck-sponsored publications in medical journals. Notably absent from these promotions was any mention that Vioxx might have caused serious ADRs.[30]

In October 2001, the FDA proposed that Vioxx carry a warning for cardiovascular events in its label. Merck refused. No pertinent labeling change was made until April 2002 when Merck finally amended the label to include, at the FDA's insistence, a "precaution" though only for those patients with a history of cardiovascular events.[31]

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[29] *McDarby, supra* at 29-30. (Merck also stressed in this release the gastrointestinal safety of Vioxx.).

[30] *Id. See also* Krumholz, *et al.*, *"What Have We Learnt From Vioxx?"* BMJ 2007; 334: 120-123.

[31] *McDarby, supra* at 45 ("Merck proposed relocation of the FDA's text to the Precautions section of the label, and to modify the text to de-emphasize the risk of Vioxx"); *Id.* at 47-48 ("The revised label for Vioxx was approved on April 11, 2002, two years after the results of the VIGOR study were known, and a 'Dear Doctor' letter substantially incorporating the information set forth in the label was circulated by Merck that same month. A review of the label demonstrates that Merck successfully obtained the FDA's consent to use of a revised label that contained no

(Continued on following page)

At about this time, two other studies, Protocols 078 and 091, also demonstrated a three-to-four times increased risk of mortality for patients taking Vioxx when compared with those taking a placebo.[32] When Merck first learned of these results, it was in the midst of negotiating a new label for Vioxx with the FDA. *Id.* Despite ongoing discussions with the FDA, Merck never gave these analyses to the FDA nor did it disclose any of this information to the medical community or patients. *See* Psaty, *supra.*

Meanwhile, when promoting Vioxx to physicians, Merck sales representatives were taught to "dodge" doctors' questions about the cardiovascular risks of the drug.[33] If the VIGOR study was brought up, they were instructed to show physicians a "Cardiovascular

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mention of cardiovascular risks in the "Warnings" section, but instead, contained a "Precaution" that limited use of Vioxx only among patients "with a medical history of ischemic heart disease" – patients whose already-diagnosed coronary artery disease was symptomatic." The label did note that: "Prospective studies specifically designed to compare the incidence of serious CV events in patients taking Vioxx versus NSAID comparators or placebo have not been performed.").

[32] *See* Memorandum, Apr. 8, 2001: "MK0955 Combined Mortality Analysis Protocol 091 + Protocol 078," at 6-7 <http://www.biostat.washington.edu/research/Rofecoxib/Ref%2014%20-%20Merck%20Statistician%20Alzheimer's%20Mortality%20Report.pdf>

[33] *McDarby, supra* at 40. ("Dodge Ball Vioxx" documents instructed sales representatives how to "dodge" obstacles that included questions about Vioxx's risk.).

Card," but not leave it with the physician. *McDarby, supra*, at 40. This card compiled data from selected studies on Vioxx that purported to demonstrate a favorable cardiovascular and mortality profile for Vioxx.[34]

At the same time, Merck either authored and/or sponsored publications in medical journals that provided misleading safety profiles for Vioxx.[35] Advocates were paid by Merck to give lectures to other doctors about Vioxx. The FDA cited some of these lectures as containing false and misleading promotions concerning the safety and efficacy of Vioxx. *McDarby*, *supra*, at 42-43.

On September 30, 2004, Merck finally withdrew Vioxx from the market after still another clinical trial, APPROVe, demonstrated a more than two-fold risk of heart attack and other cardiovascular adverse events in patients taking Vioxx as compared with a placebo.[36] During the five years Vioxx was on the

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[34] Merck & Co., Inc., "In Response To Your Questions – Once Daily Vioxx (refecoxib): Cardiovascular System – Clinical Profile in Osteoarthritis Studies" <http://www.vioxxdocuments.com/Documents/Krumholz_Vioxx/Merck2000CVcard.pdf>.

[35] *See* Krumholz, *supra*, at 120; *also see* Ross, *et al.*, *Guest Authorship and Ghostwriting in Publications Related to Rofecoxib*, JAMA 2008, 299(15): 1800-1812.

[36] Bresalier, *"Cardiovascular Events Associated with Rofecoxib in a Colorectal Adenoma Chemoprevention Trial,"* NEJM, 352: 1092-1102 (2005) and annexed *Correction*, <http://content.nejm.org/cgi/reprint/352/11/1092.pdf>.

market, over 100 million prescriptions were written for an estimated 20 million patients.[37] Applying the risk-levels seen in VIGOR and APPROVe, it has been estimated that between 88,000 and 139,000 Americans suffered Vioxx induced cardiovascular events, of whom 30-40 percent (24,000-55,600) died.[38]

C. Aprotinin (Trasylol)

Bayer Pharmaceuticals began marketing Trasylol in the 1970s. In 1987, Dr. David Royston discovered that Trasylol would reduce blood loss and the need for transfusions in repeat heart bypass surgery.[39] In December, 1993, the FDA approved Trasylol for prophylactic use during these surgeries. Fifteen years later, Trasylol was withdrawn from the market for causing kidney failure, resultant dialysis, and death.

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[37] *See In Re: Vioxx Prods. Liab. Litig.*, 501 F. Supp. 2d 776, 779 (E.D. La. 2007).

[38] *See* Graham, M.D., M.P.H., Testimony to United States Senate Committee on Finance, Nov. 18, 2004. <http://finance.senate.gov/hearings/testimony/2004test/111804dgtest.pdf>. Another estimate is that up to 320,000 cases of heart attacks and strokes occurred due to Vioxx. Topol, *"Failing the Public Health – Rofecoxib, Merck, and the FDA,"* NEJM, 351: 1707-1709 (Oct. 21, 2004) ("Given the finding in the colon-polyp trial in low-risk patients without known cardiovascular disease – an excess of 16 myocardial infarctions or strokes per 1000 patients – there may be tens of thousands of patients who have had major adverse events attributable to rofecoxib.")

[39] Royston, *et al.*, *"Effect of aprotinin on need for blood transfusion after repeat open-heart surgery,"* Lancet, 1987; ii: 1289-1291.

Before gaining approval for Trasylol, Bayer had ample warning signs regarding Trasylol's effect on kidney function. Early 1980's toxicological studies indicated Trasylol was not easily broken down by the kidneys, while other studies demonstrated severe kidney damage in test animals.[40] In 1992, a year before Trasylol was approved by the FDA, a study found that, of 20 patients administered Trasylol, 13 reported problems with kidney function.[41] Despite this information, only a minority of the 45 Trasylol clinical studies conducted prior to the FDA's approval even commented on renal function. Of these, none had sufficient numbers of patients to determine whether Trasylol exposure increased the risk of renal failure.

In August 1998, as a condition for approving amendments to the Trasylol Package Insert regarding non-kidney-related ADRs, the FDA required Bayer to conduct post-approval clinical studies, along with evaluations and analyses, as a condition for its

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[40] Fisher, *et al.*, *"High-dosage Aprotinin (Trasylol) Therapy – Is It Safe For The Kidney?"* Langenbecks Arch. Chir. 1983; 360(4): 241-9.; Fisher, *et al.*, *"Aprotinin (Trasylol) Protection – Unsuitable for Hypothermic Kidney Preservation,"* Transplantation, 1984 37(1): 115.

[41] Sundt, *et al.*, *"Renal dysfunction and intravascular coagulation with aprotinin and hypothermic circulatory arrest,"* Ann. Thorac. Surg., July 1993, 55: 1418-1424.

approval of the revised Package Insert.[42] Bayer did not conduct the clinical studies required by the FDA, nor did it conduct any evaluations or analyses that would generate clinically meaningful information about the safety of Trasylol. Between August 1998 and December 2006, no material safety information was reviewed by the FDA for inclusion in the Trasylol Package Insert.[43]

In 2006, *NEJM* published an article by Dr. Dennis Mangano that specifically analyzed the relationship between Trasylol administration and kidney failure. Mangano's study closely followed a study by Dr. Keyvan Karkouti that compared Trasylol with a competitor, tranexamic acid, and found the two were equally effective, but that only Trasylol had a significantly negative effect on renal function.[44] The Mangano study reported that study patients who were given Trasylol were more than twice as likely to have kidney failure requiring dialysis, had 55 percent more heart failures, and 181 percent more strokes. The authors advised against further use of Trasylol,

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[42] *See* FDA Center for Drug Evaluation and Research, Approval Package & Final Printed Labeling for Aprotinin <http://www.fda.gov/cder/foi/nda/98/020304s004_appltr_prntlbl.pdf>.

[43] *See* FDA Center for Drug Evaluation and Research, Approval History for Aprotinin: NDA 020304 <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory#apphist>.

[44] Karkouti, *et al.*, "*A propensity score case-control comparison of aprotinin and tranexamic acid in high-transfusion-risk cardiac surgery*," Transfusion, 2006, 46, 3: 327-338.

because safer, cheaper drug alternatives were available.[45]

On February 1, 2006, Bayer commissioned an external study to be done by i3 Drug Safety ("i3"), hoping to contradict Mangano's work. For the next eight months, Bayer kept the existence of its commissioned study by i3 secret from the public and the FDA.

In May 2006, the FDA announced that in September 2006 it would convene a meeting of its Cardiovascular and Renal Drugs Advisory Committee. The FDA asked Bayer to submit information relevant to Trasylol and specifically to address the issues raised by the Mangano and Karkouti studies. Bayer submitted voluminous information to the FDA and contacted the agency several times regarding the Trasylol meeting, but failed to disclose its commission of the i3 study.

A week before the meeting, i3 and its principal investigator Dr. Alexander Walker released the preliminary findings of their study to Bayer. The i3 study examined the medical records of approximately 67,000 patients, of whom 30,000 received Trasylol. It confirmed the findings of Karkouti and Mangano.[46]

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[45] Mangano, *et al.*, *"Risks Associated with Trasylol in Cardiac Surgery,"* NEJM, 2006, 354(4):353-65.

[46] FDA Center for Drug Evaluation and Research, Transcript of Cardiovascular and Renal Drugs Advisory Committee In Joint Session With The Drug Safety and Risk Management Advisory

(Continued on following page)

On September 21, 2006, the FDA held an Advisory Committee Meeting to discuss the safety and overall risk-benefit profile for Trasylol. After multiple presentations on the safety and efficacy of Trasylol by Bayer – again without any mention of the i3 study – the FDA Committee voted that there should be no changes to the Trasylol labeling.[47]

In response to Bayer's failure to disclose the i3 study to the FDA, Dr. Walker revealed the details and outcome of the study to the agency. The study demonstrated that Trasylol may increase the chance for death, serious kidney damage, congestive heart failure, and strokes. *Id.* Two days later, the FDA issued a second safety alert regarding the use of Trasylol and Bayer's failure to disclose the i3 study.[48] The FDA warned physicians to carefully monitor patients for the occurrence of toxicity, particularly to the kidneys, heart, or brain, and promptly report ADRs.

Finally, on December 15, 2006, that the FDA required that the Package Insert for Trasylol include additional Warnings and Precautions.[49] The FDA also

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Committee, September 12, 2007 at 22-23 <http://www.fda.gov/ohrms/dockets/AC/07/transcripts/2007-4316t1-part1.pdf>.

[47] *See* Zuckerman Spaeder LLP, "Report on Trasylol for Bayer Corporation and Bayer AG," (Aug. 1997) <http://pharma.bayer.com/html/pdf/BAYER_REPORT_FINAL_8-2007.PDF>.

[48] FDA, "Statement regarding new Trasylol data" <http://www.fda.gov/bbs/topics/NEWS/2006/NEW01472.html>.

[49] *See* FDA Approval History, *supra*.

finally sent out an alert to healthcare professionals, advising them of a change in the product label for Trasylol and stating: "[T]he new label has a more focused indication for use, a new Warning about renal dysfunction, a revised Warning about anaphylactic reactions, and a new Contraindication."[50]

In June 2007, the University of Connecticut published a study, known as the REACTS study, which showed findings almost identical to those shown in Mangano's study.[51] On November 5, 2007, a Canadian-based clinical study, known as the BART study, was released to the public. The BART study was halted in October 2007 due to an alarming death rate associated with Trasylol. The BART study showed an increased risk of death when compared with aminocaproic acid and tranexamic acid, consistent with the findings in other studies that safer, cheaper, and equally effective alternatives for Trasylol existed.[52] After the findings of the BART study were published, the FDA could not identify any specific patient population as to which it believed the

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[50] FDA, *Information for Healthcare Professionals* <http://www.fda.gov/CDER/Drug/InfoSheets/HCP/aprotininHCP.pdf>.

[51] Coleman, *et al.*, "*Evaluating the safety implications of aprotinin use: The Retrospective Evaluation of Aprotinin in Cardio Thoracic Surgery (REACTS),*" J. Thorac. Cardiovasc. Surg. 2007, 133: 1547-1552.

[52] Fergusson, *et al.*, "*A comparison of aprotinin and lysine analogues in high-risk cardiac surgery,*" NEJM, 358(22): 2319-2331 (2008).

benefit of using Trasylol outweighed the risks. On May 15, 2008, years after first becoming aware of the risks of Trasylol, Bayer suspended worldwide sales of Trasylol following an FDA request to remove the drug from the market for safety reasons.

Between 1999 and 2005, Bayer generated over $935 million in revenue from sales of Trasylol with over $353 million in 2005.[53] Bayer forecast that Trasylol would some day generate upwards of $600 million annually. In February 2008, on the CBS program *60 Minutes*, Dr. Mangano estimated that, of the 431,000 people who took the drug after he published his analysis, 22,000 lives could have been saved.[54] While the true number of those who died as a result of Trasylol administration will never be known, given Bayer's own estimate that, through 2005, 4.3 million patients had been given Trasylol, it is possible that another 220,000 died as a result of using Bayer's product.

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[53] *See* Bayer Annual Reports (Form 20-F) (converted from euros on Aug. 6, 2008) <http://sec.gov/Archives/edgar/data/1144145/000115697302000306/f00360e20vf.txt>; <http://sec.gov/Archives/edgar/data/1144145/000132693206000060/0001326932-06-000060-index.htm>; and <http://sec.gov/Archives/edgar/data/1144145/000115697303000973/f00582e20vf.htm>.

[54] "One Thousand Lives A Month," *60 Minutes*, CBS, Feb. 17, 2008, <http://www.cbsnews.com/stories/2008/02/14/60minutes/main3831900.shtml>.

III. PETITIONER'S POLICY ARGUMENTS IN FAVOR OF PREEMPTION LACK ANY EMPIRICAL BASIS

The discussions above related to Pondimin/Redux, Vioxx, and Trasylol demonstrate the extent to which pharmaceutical manufacturers have delayed necessary warnings when substantial profits are at risk. The import of this is rather striking in light of Petitioner's/*Amici*'s two major arguments in support of preemption: that the true risks and benefits of prescription drugs will be obscured by too many warnings ("over-warning") and that product liability litigation has adversely affected the economics of the pharmaceutical industry and its ability to provide drugs that are needed. Neither is true.

A. The Risk of "Over-warning" is More Theoretical Than Real

Petitioner's/*Amici*'s primary policy justification for preemption is that litigation forces manufacturers to add unnecessary warnings, which allegedly confuse both patients, who stop using necessary drugs, and medical practitioners, who fail to prescribe optimal drug therapies. Petitioner/*Amici* also maintain that drug manufacturers will be punished by the FDA adding unnecessary warnings in response to failure-to-warn lawsuits. Notably, however, despite seventy years of drug regulation by the FDA, neither Petitioner nor

its *amici* cite to a single example where a drug manufacturer was punished for over-warning.[55]

Nor is there any evidence that "overwarning" has resulted in underutilization of prescription drugs. While Petitioner/*Amici* (*see, e.g.,* WLF at 14-15) cite to studies where pharmaceutical therapies might have underutilized, the cited references do not attribute the underutilization to "over-warnings" added in response to product liability lawsuits.

Nor have Petitioner/*Amici* provided any evidence that medical professionals would be better off with fewer warnings. In advancing this argument, Petitioner/*Amici* ignore the fact that prescription drug labeling is directed to a sophisticated physician audience that is well able to comprehend a thorough product insert. Medical practitioners have consistently requested complete warnings, albeit formatted in a user-friendly fashion.[56]

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[55] *See* Nagareda, *"FDA Preemption: When Tort Law Meets the Administrative State,"* J. Tort L. art. 4 at 32, n. 127, citing *McNellis v. Pfizer, Inc.*, No. Civ. 05-1286 (JBS), 2005 WL 3752269 (D. N.J. 2005), *rev'd on other grounds, Colacicco v. Apotex Inc.*, 521 F.3d 253 (3rd Cir. 2008) (noting submission of former FDA official's affidavit asserting lack of awareness of any instance in which the agency had deemed misbranded a drug whose labeling included additional statements beyond those required as part of FDA approval).

[56] PhRMA at 15 cites to a national survey of physicians described at 65 Fed. Reg. 81,082-84. The complaints referenced did not go to "over-warning" but rather formatting for ease of use.

In fact, close scrutiny of Petitioner/*Amici*'s briefing reveals a lack of even putative instances where "over-warning" affected prescription drug usage. Their examples include: 1) warnings not required by the tort system but by the FDA itself regarding the consumption of fish (WLF at 17-19); 2) third generation birth control pills that were challenged not by the tort system but by the consumer group Public Citizen in a petition to the FDA (WLF at 20-22); and 3) a controversy over vaccinations sparked not by a lawsuit but by an article spread through the popular press (PhRMA at 23-24).[57] Even if "over-warning" were truly a problem with respect to drug underutilization, these examples demonstrate that lawsuits play only a minor role at best in fueling the public's perceptions.

Indeed, in over 400 pages of briefing, Petitioner/*Amici*'s pharmaceutical "over-warning" examples reference just one class of drugs, SSRIs, and two individual drugs, Norplant for birth control, and Bendectin. Even in the case of the drug most frequently mentioned, Bendectin,[58] the alleged lack of a replacement therapy speaks primarily to the small market for drugs designed to alleviate non-severe

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[57] Virtually all vaccine cases are heard in "vaccine court" pursuant to the no-fault provisions of The National Childhood Vaccination Injury Act rather than through the civil justice system. *See* National Childhood Vaccination Injury Act, 42 U.S.C. § 300aa-1, *et seq.*

[58] *See* Calfee at 15; DRI at 31-32; PhRMA at 23-24.

"morning sickness" (severe "morning sickness," *hyperemesis gravidarum*, requires hospitalization). Moreover, in contrast to the withdrawn drugs discussed at length above, Petitioner/*Amici* do not point to a single article that states that the failure to use Bendectin caused any long-term damage to either a mother or her fetus.

Furthermore, it is extraordinary that Petitioner/*Amici* would repeatedly return to Bendectin as their best example of "over-warning" justifying preemption when this Court has already opined in a Bendectin case regarding the appropriate manner in which courts should evaluate the merits of pharmaceutical failure-to-warn cases. *See Daubert v. Merrell-Dow Pharmaceuticals, Inc.*, 509 U.S. 579 (1993). There, this Court mandated judicial scrutiny over the necessary pharmacological, toxicological, and often epidemiological expert testimony required to meet the evidentiary requirements for medical and scientific causation related to the condition requiring a warning in drug-related injury cases. *See also General Electric Co. v. Joiner*, 552 U.S. 136 (1997)[59]; *Weisgram v. Marley*, 528 U.S. 440, 442 (2000) ("Since *Daubert* . . . parties relying on expert evidence have had notice of the exacting standards of reliability such evidence

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[59] NEJM has previously stated that this is the appropriate screening mechanism for meritorious claims. *See* "Brief *amici curiae* of the New England Journal of Medicine and Marcia Angell, M.D., in support of neither petitioners nor respondents" filed in *Joiner*, *supra*.

must meet.") Twenty-eight states, including Vermont, now apply *Daubert* or a similar test, six apply *Daubert* factors, and all states have some mechanism for scrutinizing the admissibility of scientific evidence before it is presented to a jury. 90 ALR 5th 453.[60] To argue that warnings are being required for random "unsubstantiated" outcomes ignores fifteen years of post-*Daubert* jurisprudence.[61]

B. Petitioner's/*Amici*'s Economic Arguments for Preemption Are Little More Than a General Indictment of the Entire Product Liability System

All of Petitioner's/*Amici*'s principal economic policy arguments in favor of federal preemption are routinely made by manufacturers of all products: *i.e.*, that subjecting manufacturers to tort liability creates a risk of over-deterrence that might result in excessive risk control, stifle innovation, and impose unreasonable costs, including subjecting them to the costs of liability defense and insurance. In making these time-worn arguments, Petitioner/*Amici* do not supply any

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[60] *Daubert* has led all state and federal courts to increase their scrutiny over such scientific evidence regardless of the standard applied. *See* Cheng, *et al.*, *"Does Frye or Daubert Matter?"* 91 Va. L. Rev. 471 (2005).

[61] Note that PhRMA at 7, n.2, excises a pre-*Daubert* quote from 1979.

empirical evidence to explain why the pharmaceutical industry uniquely deserves such blanket protection.[62]

The prescription drug industry earns global revenues of more than $700 billion per year, an increase of $178 billion over the last five years.[63] Petitioner/*Amici*'s argument that tort suits have led Americans to underutilize prescription drugs or companies to limit product development is baseless. As of 2004, Americans were responsible for $248 *billion* in pharmaceutical sales, accounting for nearly 45 percent of all revenue worldwide.[64] Despite representations of a so-called explosion of stifling litigation, the pharmaceutical market has grown, not shrunk. And it has done so dramatically: In 2007 alone, there were approximately 445 million more prescriptions written than in 2003.[65]

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[62] Notably, their economic-based arguments are not based upon preemption, as all of these arguments would be precisely the same if the FDA didn't exist.

[63] IMS Health, "IMS Health Reports Global Prescription Sales Grew 6.4 Percent in 2007, to $712 Billion," April 16, 2008 <http://www.imshealth.com/portal/site/imshealth/menuitem.fc2127a7c34504dc88f611019418c22a/?vgnextoid=38bd4822d7699110VgnVCM10000071812ca2RCRD&vgnextchannel=41a67900b55a5110VgnVCM10000071812ca2RCRD&vgnextfmt=default>.

[64] IMS Health, "IMS Reports 2004 Global Pharmaceutical Sales Grew 7 Percent to $550 Billion," Mar. 9, 2005 <http://www.imshealth.com/ims/portal/front/articleC/0,2777,6599_3665_71496463,00.html>.

[65] *See* IMS Health, 2007 Channel Distribution by U.S. Dispensed Prescriptions <http://www.imshealth.com/deployedfiles/ims

(Continued on following page)

Meanwhile, liability costs referenced by Petitioner/*Amici* pale in comparison to promotional costs. Drug companies now spend over $29 billion annually just to promote their products, including $11.4 billion on advertising.[66] Nothing demonstrates this better than the case of Vioxx. In 2000, Vioxx was the number one direct-to-consumer advertised drug at $160 million – larger than the campaigns that year for Pepsi and Budweiser.[67]

IV. UNDER THIS COUNTRY'S REGULATORY FRAMEWORK, EFFECTIVE MONITORING OF DRUG RISKS REQUIRES A ROBUST TORT SYSTEM

Product liability lawsuits and the FDA have peacefully coexisted for seventy years for one simple reason: they have complementary, rather than conflicting, goals. The tort system complements the federal regulatory structure by providing a mechanism for compensating victims of hazardous drugs. Product liability litigation provides the FDA with key information unearthed in litigation that the agency can use to better protect the public from unsafe and

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health/Global/Content/Document/Top-Line%20Industry%20Data/2007%20Channel%20Distribution%20by%20RXs.pdf>.

[66] Donohue, *et al.*, "*A Decade of Direct-to-Consumer Advertising of Prescription Drugs*," 357 NEJM 673, 674 (2007).

[67] Nat'l Inst. for Health Care Mgmt., *Prescription Drugs and Mass Media Advertising*, 2000, at 5 (2001) <http://www.nihcm.org/~nihcmor/pdf/DTCbrief2001.pdf>.

inadequately labeled drugs. At the same time, the tort system and the FDA are similarly constrained. Whereas the FDA, as a regulatory body, weighs the risks against the benefits of a drug, in "failure-to-warn" litigation most state courts require a similar balancing between the cost of care owed to a patient versus the prospective harm.[68] As former FDA chief counsel Margaret Porter wrote, "FDA product approval and state tort liability usually operate independently, each providing a significant, yet distinct, layer of consumer protection."[69]

Frequently, serious safety issues come to light only after a drug has entered the market. However, the FDA, unlike most other federal agencies, has no subpoena power and, therefore, only knows what a manufacturer chooses to reveal to it. Companies have no obligation to provide the FDA with internal company evaluations of a drug's performance in the

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[68] Judge Learned Hand described his formula in *United States v. Carroll Towing Co.*, 159 F.2d 169, 173, *reh'g denied*, 160 F.2d 482 (2d Cir. 1947), where he compared the cost of precautions with the expected loss. *See* Gilles, *"On Determining Negligence: Hand Formula Balancing, The Reasonable Person Standard, and the Jury,"* 54 Vand. L. Rev. 813, 816-22 (2001) (describing the broad use, as well as complications, in applying Hand's formula).

[69] Porter, *"The Lohr Decision: FDA Perspective and Position,"* 52 Food & Drug L.J. 7, 9 (1997).

market, let alone the company's internal documents frankly assessing a drug's safety profile.[70]

By contrast, state tort law provides essential information-gathering tools, which can be an important avenue by which the health care community learns of safety and efficacy information.[71] Through the process of discovery, litigation has regularly uncovered information about drug toxicity that would otherwise not have been known, such as the type discussed above in the cases of Pondimin/Redux and Vioxx. Discovery in both instances revealed that the companies knew much more about their product's safety problems than they ever revealed to the FDA, the medical profession, or the public.

Secondly, by levying damages for certain kinds of harm, tort law can provide powerful disincentives to risky behaviors, as well as aid the FDA in its mission. In these days of budget cutbacks, with declining resources to pay for inspections, investigations, and legal actions, the products liability system becomes a vital element in promoting compliance with the FDA's safety goals. Even the threat of civil liability is a vital bargaining tool for the FDA in pressuring companies

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[70] *See* Kesselheim, *et al.*, *"The Role of Litigation in Defining Drug Risks,"* 297 JAMA 308, 310 (2007).

[71] *See* Struve, *"The FDA and the Tort System: Postmarketing Surveillance, Compensation and the Role of Litigation,"* 5 Yale J. Health Policy & Ethics 587, 591 (2005) (noting preemption removes opportunity for litigation system to aid in effort to monitor product safety).

to amend labels to warn of newly understood risks. If pharmaceutical companies were granted almost complete immunity by virtue of federal preemption, they would have minimal incentive to report or warn of the adverse health effects of their drugs. In fact, given that pharmaceutical companies have been known to equate increased warnings with a loss of sales, they would have an incentive to delay warnings as long as possible. As has been shown, certain pharmaceutical companies have already proven themselves unwilling to prioritize safety over profits, even when faced with the threat of civil liability.[72] It is chilling to imagine how such companies might conduct themselves if the threat of tort liability for dangerous drugs were eliminated entirely by virtue of federal preemption.

Finally, the civil justice system has the ability to improve the lives of injured patients and their families in ways that the FDA cannot. It can provide protection in cases like the examples of Trasylol and Vioxx, where the FDA was late in acting. Meritorious lawsuits can transfer the obligation to pay for the losses caused by tragic ADRs from this country's

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[72] *See* Davis, "*The Battle over Implied Preemption: Products Liability and the FDA*," 48 B.C. L. Rev. 1089, 1095 (2007); O'Steen, "*The FDA Defense: Vioxx® and the Argument Against Federal Preemption of State Claims for Injuries Resulting from Defective Drugs*," 48 Ariz. L. Rev. 67, 96 (2006); Schwartz, "*Regulatory Standards and Products Liability: Striking the Right Balance Between the Two*," 30 U. Mich. J.L. Rev. 431 (1997).

healthcare system to pharmaceutical companies. As written so bluntly by FDA counsel Porter, the tort system remedies the "harsh implications" of the FDA's inability to provide "recourse for consumers injured by defective" drugs. Porter, *supra* at 9.

CONCLUSION

Because the preemption of state failure-to-warn claims involving prescription drugs would threaten this nation's public health by eliminating a necessary counterpart to the FDA, *Amici* urge this Court to affirm the decision of the court below.

Respectfully submitted,

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APPENDIX "A"

TRADEMARK NAME	MARKET NAME	PURPOSE	FIRST SOLD	WITH-DRAWN	REASON WITHDRAWN
Amineptine	Survector	anti-depressant	1978	1999	hepatoxicity
Aprotinin	Trasylol	heart bypass bleeding reduction	1993 (for use)	2007	kidney damage; death
Astemizole	Hismanal	edema and antihistamine	1988	1999	fatal heart problems
Azaribine	Triazure	severe arthritis	1975	1977	embolisms
Benoxaprofen	Oraflex	anti-inflammatory	1982	1982	cholestatic jaundice; death
Bromfenac	Duract	pain	1997	1998	liver failure
Butamben	Efocaine	local anesthetic	1952	1964	paraplegia
Cerivastatin	Baycol	cholesterol reduction	1997	2001	rhabdomyolysis; death
Chlormadinone acetate	Estalor-21, C-Quens	oral contraceptive	1965	1972	emboli
Cisapride	Propulsid	gastro-esophageal reflux	1993	2000	arrhythmias; death
Dexfenfluramine	Redux	appetite suppressant	1996	1997	pph; cardiac valvulopathy
Diamthazole dihydrochloride	Asterol	antifungal agent	1951	1977	neurotoxicity
Diethylstilbestrol (DES)	Stilphostrol, etc.	multiple – most vaginally related	1941	tablets 1975; gradually limited	birth defects; vaginal adenocarcinoma in daughters
Encainide	Enkaid	arrhythmia	1986	1991	increased risk of death from arrhythmia

TRADEMARK NAME	MARKET NAME	PURPOSE	FIRST SOLD	WITH-DRAWN	REASON WITHDRAWN
Etretinate	Tigason	psoriasis	1985	1998	high risk of birth defects
Fenfluramine	Pondimin	appetite suppressant	1973	1997	PPH; cardiac valvulpathy
Flosequinan	Manoplax	congestive heart failure	1992	1993	increased hospitalization; death
Grepafloxacin	Raxar	pneumonia; bronchitis	1997	1999	arrhythmia; death
Hydro-morphone	Palladone	analgesia; cough suppressant	2004	2005	fatal when taken with alcohol
Levomethadyl	Orlaam	opiate addiction	1995	2004	cardiac arrest
Nomifensine	Merital	anti-depressant	1985	1986	kidney/liver toxicity; death
Pergolide Mesylate	Permax	Parkinson's symptoms	1988	2007	heart valvulopathy
Mepazine	Pacatal	anesthesia	1955	1970	seizures; intestinal paralysis;
Mibefradil	Posicor	hypertension; chronic angina	1997	1998	congestive heart failure
Oxyphenisatin	Laverna, etc.	laxative	1955	1973	liver failure
Pemoline	Cylert	ADHD and narcolepsy	1975	2005	liver failure
Phenformin hydrochloride	Fenermin	Type-2 diabetes	1959	1977	fatal lactic acidosis
Pipamazine	Mornidine	vomiting; nausea	1959	1969	kidney lesions
Rapacuronium	Raplon	anesthesia	1999	2001	respiratory spasms; death

TRADE-MARK	MARKET NAME	PURPOSE	FIRST SOLD	WITH-DRAWN	REASON WITHDRAWN
Reserpine	Reserpoid, Rau-Sed	hypertension	1954	1977	irregular heartbeat; hearing loss; vision problems
Rofecoxib	Vioxx	pain; arthritis	1999	2004	heart attack; stroke; death
Sulfadi-methoxine	Madri-cidin	respiratory infections	1959	1966	Stevens-Johnson syndrome
Sulfathiazole	Tresamide	antimicrobial	1939	1970	kidney and liver damage; death
Suprofen	Suprol	anti-inflammatory	1985	1987	kidney toxicity
Technetium fanolesomab	Neutro-Spec	diagnosing appendicitis	2004	2005	cardiopulmonary failure; death
Tegaserod Maleate	Zelnorm	irritable bowel; constipation	2002	2007	serious heart problems
Temafloxacin	Omniflox	infections	1992	1992	anemia; death
Terfenadine	Seldane	antihistamine	1985	1998	fatal arrhythmia
Thalidomide	Multiple	sedative -- hypnotic	1956	1962 (re-stricted)	severe limb birth defects
Tienilic Acid	Ticrynafen	anti-hypertensive	1979	1980	kidney failure; liver toxicity
Troglitazone	Rezulin	Type-II diabetes	1997	2000	liver toxicity
Trovafloxacin	Trovan	serious infection	1997	1998 (re-stricted)	liver toxicity
Urethane	Profenil	muscle relaxant	1976	1977	carcinogenicity
Valdecoxib	Bextra	arthritis, etc.	2001	2005	Stevens Johnson syndrome; heart attack
Zomepirac	Zomax	pain	1981	1983	fatal and near fatal anaphylactic reactions

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WYETH,

Petitioner,

v.

DIANA LEVINE,

Respondent.

On Writ of Certiorari to
the Vermont Supreme Court

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QUESTION PRESENTED

Whether the prescription drug labeling judgments imposed on manufacturers by the Food and Drug Administration ("FDA") pursuant to FDA's comprehensive safety and efficacy authority under the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 301 *et seq.*, preempt state law product liability claims premised on the theory that different labeling judgments were necessary to make drugs reasonably safe for use.

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INTEREST OF AMICI CURIAE

The Pharmaceutical Research and Manufacturers of America ("PhRMA") is a voluntary, nonprofit association that represents the country's leading research-based pharmaceutical and biotechnology companies.[1] PhRMA's members are dedicated to discovering medicines that enable patients to lead longer, healthier, and more productive lives. Member companies are the source of a majority of all new medicines that are discovered and marketed. In the last decade, PhRMA's members invested approximately $300 billion to develop new medicines. *See* PhRMA, *Pharmaceutical Industry Profile 2007* 42 (2007). New medicines account for 40 percent of the lifespan increase between 1986 and 2000. *See* Frank R. Lichtenberg, *The Impact of New Drug Launches on Longevity: Evidence From Longitudinal, Disease-Level Data From 52 Countries, 1982-2001* 21 (Nat'l Bureau of Econ. Research, Working Paper No. 9754, 2003).

The Biotechnology Industry Organization ("BIO") is the world's largest biotechnology organization, providing advocacy, business developments, and

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[1] Each party has consented to the filing of this brief and the parties' letters of consent have been lodged with the Clerk. Pursuant to Supreme Court Rule 37.6, no counsel for a party authored this brief in whole or in part, and no party or counsel for a party made a monetary contribution intended to fund the preparation or submission of this brief. A list of PhRMA's members is available at http://www.phrma.org. BIO's members are listed at http://www.BIO.org.

communications services for more than 1,150 members worldwide. BIO's mission is to champion biotechnology and advocate for its member organizations, both large and small. BIO members are involved in research and development of innovative healthcare technologies. Corporate members range from entrepreneurial companies developing a first product to Fortune 100 multinationals. BIO also represents state and regional biotechnology associations, service providers to the industry, and academic centers.

Members of PhRMA and BIO closely monitor legal issues that affect the entire industry and often offer their perspectives in cases raising such issues. The issues in this case are especially significant. Federal preemption issues arise in tens of thousands of product-liability lawsuits faced by members of PhRMA and BIO. These state-law suits undermine uniform regulation of pharmaceutical labeling by the federal Food and Drug Administration ("FDA"). Such suits also pose a threat to public health in two significant ways: *first*, by encouraging unduly risk-averse drug labeling and, at the extreme, manufacturer decisions to withdraw medicines from the market or not introduce them at all; and *second*, by discouraging physicians and patients from prescribing and using beneficial medicines because of warnings about unsubstantiated risks.

SUMMARY OF ARGUMENT

The Vermont Supreme Court, over a vigorous dissent by its Chief Justice, upheld a judgment of

nearly $7 million against the manufacturer of an FDA-approved medicine. The manufacturer was held liable because the medicine's labeling failed to contraindicate a method of injection that FDA had expressly permitted. The labeling included carefully worded instructions and warnings approved by FDA, which had reviewed the drug's risks and benefits for nearly a half-century. The Court should reverse the Vermont court's decision on the ground that Respondent's state-law claims are preempted by federal law.

1. State-law tort suits challenging the adequacy of FDA-approved prescription drug labeling pose significant risks to public health and to FDA's ability to accomplish its mission. Such suits, which have increased in number in recent years, typically focus on the very question that is a primary FDA focus in regulating medical products: evaluating and managing the risks associated with prescription medications. As a result, juries in state-law tort suits often are required to second-guess FDA's balancing of the risks and benefits of a prescription medicine. The threat of liability under state law encourages manufacturers to warn physicians and patients about risks that are speculative and scientifically unsupported. This ultimately dilutes the impact of scientifically valid warnings and discourages physicians and patients from using beneficial drugs. In addition, state-law tort actions can drive beneficial drugs off the market and deter the development of new drugs that would enhance patient health and safety.

2. The Vermont Supreme Court's decision is at odds with a core premise of the Supremacy Clause: State law cannot require what federal law prohibits. Absent new scientific information, federal regulations prohibit a manufacturer from changing prescription drug labeling without prior FDA approval. In this case, FDA knew of and considered the relevant risk over a period of decades, and approved carefully-crafted warnings and instructions designed to minimize those risks while encouraging beneficial drug use. While conceding that preemption would result "if the FDA intended . . . to prohibit any language strengthening the original warning," the Vermont Supreme Court erroneously concluded that there was no preemption because FDA had not rejected the *precise* warning sought by the plaintiff.

In addition, Respondent's state-law claims pose a serious obstacle to the objectives of the Federal Food, Drug, and Cosmetic Act by allowing a jury to second-guess FDA's careful balancing of the risks and benefits of prescription medicines. In approving drug labeling, FDA does not merely set minimum safety standards. Instead, it balances the expected therapeutic gain from a medicine against the risk entailed by its use. When juries, focusing only on the particular plaintiff before them, require warnings about unsubstantiated risks, they undermine the purpose of the FDCA by discouraging physicians and patients from using beneficial medicines.

If allowed to stand, the Vermont Supreme Court's "magic words" requirement will encourage

pharmaceutical companies to inundate FDA with requests for labeling changes to ensure that federal regulators have been presented with every potential labeling permutation. These requests, driven by the need to create a record for future litigation rather than by science, will distract agency scientists from their core mission of reviewing the safety and effectiveness of prescription medications.

ARGUMENT

I. State-Law Tort Claims Challenging Prescription Drug Labeling Undermine FDA Decisionmaking And Pose A Threat To Public Health.

A. FDA's Authority To Approve Drug Labeling Is Central To The Agency's Balancing Of Risks And Benefits.

The Federal Food, Drug, and Cosmetic Act ("FDCA"), 21 U.S.C. § 301 *et seq.*, creates one of the world's most demanding prescription drug approval regimes.[2] On average, it takes nearly twelve years for a new drug to be developed and approved by FDA. *See* Joseph A. DiMasi et al., *The Price of Innovation: New Estimates of Drug Development*

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[2] In this brief, references to prescription drugs include drugs licensed as biological products pursuant to Section 351 of the Public Health Service Act, 42 U.S.C. § 262. These drugs are subject to the FDCA prohibition on misbranding, 21 U.S.C. § 352, as well as the prescription drug labeling regulations and regulations governing changes to an approved biologics license application, *see* 21 C.F.R. §§ 201.56-57, 601.12.

Costs, 22 J. Health Econ. 151, 164-66 (2003). A new drug application ("NDA") must include "full reports of investigations which have been made to show whether or not such drug is safe for use and whether such drug is effective in use" as well as "labeling proposed to be used for such drug." 21 U.S.C. § 355(b)(1)(A), (F). An NDA is approved only if FDA determines the drug is both safe and effective under the conditions described in the proposed labeling. *Id.* § 355(c), (d).

FDA's determination that a drug is safe and effective does not mean that the drug is risk-free. "Few if any drugs are completely safe in the sense that they may be taken by all persons in all circumstances without risk." *United States v. Rutherford*, 442 U.S. 544, 555 (1979). Instead, just as with medical devices, the FDA confronts a more complex question in regulating medicines: "How many more lives will be saved by a [medicine] which, along with its greater effectiveness, brings a greater risk of harm?" *Riegel v. Medtronic, Inc.*, 128 S. Ct. 999, 1008 (2008). As the Court noted in *Riegel*, FDA answers this question by systematically evaluating all evidence of a medicine's benefits and risks; a jury, in contrast, focuses on information pertinent to an individual plaintiff. *Id.*

The centerpiece of FDA's expert weighing of risks and benefits is the medicine's labeling. *See* 21 U.S.C. § 355(d), (e). By providing a coordinated set of instructions to physicians, including warnings and contraindications calibrated to the best scientific evidence, FDA achieves a balance in communicating

information about the benefits and risks of a drug. Consistent with this approach, FDA requires the warnings in prescription drug labeling to be supported by "reasonable evidence of an association of a serious hazard with the drug." 21 C.F.R. § 201.80(e).[3]

FDA's authority over prescription drug labeling is conferred by the FDCA, which prohibits the introduction into commerce of unapproved new drugs as well s "misbranded drugs," 21 U.S.C. §§ 331(a), (d), and which provides that a drug is "misbranded" if its labeling is "false or misleading in any particular," or if its labeling lacks "adequate directions for use," *id.* § 352(a), (f). Congress has given FDA comprehensive authority to regulate drug labeling by making labeling a fundamental component of the NDA, and by requiring that approval of an NDA must be based on an FDA finding that the drug is safe and effective for use "*under the conditions prescribed, recommended, or suggested in the proposed labeling thereof.*" *Id.* § 355(b)(1)(F), (d) (emphasis added). In addition,

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[3] *See also* 21 C.F.R. § 201.57(c)(6)(i) (warnings must be supported by "reasonable evidence of a causal association with a drug."); Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products, 71 Fed. Reg. 3,922, 3,932 (Jan. 24, 2006) (inclusion of statement that "FDA has considered and found scientifically unsubstantiated" would "render the drug misbranded under the act (21 U.S.C. 352(a) and (f))"); *id.* at 3,935 ("additional disclosures of risk information can expose a manufacturer to liability under the act if the additional statement is unsubstantiated or otherwise false or misleading").

Congress has given FDA exclusive authority to enforce the requirement that drug labeling not be false or misleading. *See id.* § 352(a). Federal law subjects manufacturers to severe civil and criminal penalties for misbranding and for distributing a new drug without an approved NDA. *See id.* § 332 (injunctions); *id.* § 333(a) (criminal penalties, including fines and imprisonment); *id.* § 334 (seizure of product). Similar penalties apply if a manufacturer improperly withholds information from FDA or makes false statements to the agency. *Id.* §§ 332, 333.

In implementing this authority, FDA extensively regulates prescription drug labeling. The package insert for a new drug must be approved word-for-word by FDA before a drug can come to market. *See* 21 C.F.R. § 314.105(b); *see also* Supplemental Applications Proposing Labeling Changes for Approved Drugs, Biologics, and Medical Devices, 73 Fed. Reg. 2,849, 2,849 (proposed Jan. 16, 2008) ("Supplemental Applications") ("FDA's review and prior approval of both the product and its proposed labeling is a necessary condition of lawful distribution of the product in interstate commerce"). In this case, FDA directed Petitioner that the "final printed labeling" for Phenergan "must be identical" to the labeling approved by FDA. Pet. App. 165a.

Once FDA has approved the labeling, federal law generally prohibits the manufacturer from making any "[c]hange in labeling" unless the manufacturer applies for a change and FDA approves the application. *See* 21 C.F.R. § 314.70(b)(2)(v)(A). In

limited circumstances, a manufacturer is permitted by FDA's regulations to change a drug's labeling at the same time it submits an application "[t]o add or strengthen a contraindication, warning, precaution, or adverse reaction," or "[t]o add or strengthen an instruction about dosage and administration that is intended to increase the safe use of the drug product." *Id.* § 314.70(c)(6)(iii)(A), (C). FDA has long interpreted this "changes being effected" (or "CBE") exception as applicable only to "concerns about *newly discovered* risks" and "important *new information* about the safe use of a drug." New Drug and Antibiotic Regulations, 47 Fed. Reg. 46,622, 46,623, 46,625 (proposed Oct. 19, 1982) (emphasis added).

When a manufacturer changes a warning without prior FDA approval, FDA reviews the revised labeling and may bring an enforcement action for making an unauthorized change or for adding statements that make the labeling false or misleading. *See* Supplemental Applications, 73 Fed. Reg. at 2,849. For these reasons, as a former FDA Chief Counsel has explained, "[t]he actual freedom of manufacturers unilaterally to change the package insert is minimal." Richard M. Cooper, *Drug Labeling & Products Liability: The Role of the Food & Drug Administration*, 41 Food Drug Cosm. L.J. 233, 236 (1986).

B. The Volume Of State-Law Tort Litigation Challenging FDA-Approved Labeling Has Expanded Significantly.

Just as drug labeling is the centerpiece of FDA's weighing of risks and benefits, it is also the focal point of state-law tort claims against pharmaceutical companies. Nearly every state recognizes that prescription drugs inherently carry a degree of risk but also provide an essential societal benefit. Therefore, pharmaceutical liability under state law generally hinges on whether the company adequately warned of knowable risks. *See, e.g., Vitanza v. Upjohn Co.*, 778 A.2d 829, 837-38 (Conn. 2001); *Rogers v. Miles Labs., Inc.*, 802 P.2d 1346, 1353 (Wash. 1991); *Grundberg v. Upjohn Co.*, 813 P.2d 89, 92 (Utah 1991); *Feldman v. Lederle Labs.*, 479 A.2d 374, 385 (N.J. 1984) (in pharmaceutical context, "strict liability analysis becomes almost identical to negligence analysis in its focus on the reasonableness of the defendant's conduct"); *see also Brown v. Super. Court*, 751 P.2d. 470, 476 (Cal. 1988) (noting that this approach "has been adopted in the overwhelming majority of jurisdictions that have considered the matter"). The state-law approach is summarized in comment k to Section 402A of the Restatement (Second) of Torts:

> There are some products which, in the present state of human knowledge, are quite incapable of being made safe for their intended and ordinary use. These are especially common in the field of drugs . . . . The seller of such products, again with the

> qualification that they are properly prepared and marketed, and proper warning is given, where the situation calls for it, is not to be held to strict liability for unfortunate consequences attending their use, merely because he has undertaken to supply the public with an apparently useful and desirable product, attended with a known but apparently reasonable risk.

Restatement (Second) Torts § 402A cmt. k (1965).

Thus, a manufacturer's liability under state tort law frequently is determined by the content of the drug's labeling — the very instructions and warnings that are carefully calibrated through FDA's regulatory process. As such, state-law claims against drug manufacturers often invite juries to second-guess FDA's decisions regarding prescription drug labeling. During the trial in this case, for instance, plaintiff's counsel explicitly asked the jury to second-guess FDA's safety determination: "Thank God we don't rely on the FDA to . . . make the safe[ty] decision. You will make the decision. . . . The FDA doesn't make the decision, you do." J.A. 211-12.

In recent years, there has been a sharp increase in the number of state-law tort suits in which juries are asked to second-guess FDA's determinations concerning the appropriate warnings and instructions about pharmaceutical risks. Rather than challenging the absence of any warning about the risk at issue, many of these state-law suits – including this case – involve situations in which FDA

has explicitly considered the risk at issue and approved labeling that expressly addresses the risk.[4]

In 2001, roughly 2,700 pharmaceutical product-liability cases asserting state-law failure to warn or related claims were litigated in federal court. Lisa Girion, *State Vioxx Trial is Set as Drug Suits Boom*, L.A. Times, June 27, 2006, at C1. That number rose to 17,000 in 2005, accounting for "more than a third of all product filings in federal courts" and "outnumbering asbestos, tobacco and auto safety claims by a widening margin since 2002." *Id.* Currently, twenty federal multidistrict litigations challenging the adequacy of FDA-approved drug labeling are pending in federal court; all but one began in 2000 or later. *See* Jud. Panel on Multidistrict Litig., *Distribution of Pending MDL Dockets* (May 13, 2008), *available at* http://www.jpml.uscourts.gov. By contrast, a recent study concluded that in the forty-year span between 1960 and 1999, there were only seven mass tort actions involving FDA-approved medicines. *See*

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[4] *See, e.g., Kelly v. Wyeth*, No. 20033314F, 2007 WL 1302589, at *6 (Mass. Super. Ct. Apr. 12, 2007) (denying defendant's motion for summary judgment because, although labeling warned of risk of akathisia, plaintiff alleged that "the risk of akathisia was much greater than that which was represented on the label"); *Smith v. Johnson & Johnson Co.*, No. 108901/01, 2004 WL 2964419, at *5 (N.Y. Sup. Ct. Nov. 22, 2004) (denying defendant's motion for summary judgment because, although labeling warned of cardiac arrest risk, plaintiff's labeling expert opined that warning "failed to place physicians on notice" that cardiac arrest could occur in patients not taking other drugs and without preexisting heart problems).

Deborah R. Hensler, *Has the Fat Lady Sung? The Future of Mass Toxic Torts*, 26 Rev. Litig. 883, 897 tbl. 1 (2007).[5]

Challenges to FDA-approved labeling affect the entire industry and target entire classes of medicines. FDA-approved labeling has been challenged in significant litigation over nearly a dozen antidepressants and other central nervous system medicines, at least four different types of weight loss drugs, numerous hormone replacement therapies, diabetes treatments, osteoporosis medicines, and an additive used in multiple vaccines.[6]

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[5] Similar increases have occurred in the state courts. For example, eight of the twelve consolidated actions designated as Mass Torts by the New Jersey courts involve challenges to FDA-approved labeling for prescription drugs. *See* N.J. Judiciary, *Mass Tort Information Center*, *at* http://www.judiciary.state.nj.us/mass-tort/index.htm (last visited May 30, 2008) ("*NJ Mass Torts*").

[6] *See* Jud. Panel on Multidistrict Litig., *Distribution of Pending MDL Dockets* (May 13, 2008), *available at* http://www.jpml.uscourts.gov (antidepressants and CNS products Serzone, Paxil, Celexa, Lexapro, Seroquel, Mirapex, Neurontin, Zyprexa; weight loss drugs meridia, phentermine, fenfluramine, and dexfenfluramine; and hormone replacement therapy Prempro and Ortho-Evra); *NJ Mass Torts*, *supra* (anti-psychotic drugs Risperdal, Seroquel, and Zyprexa; and synthetic hormones manufactured by "several pharmaceutical companies"); *Sykes v. Glaxo-Smith Kline*, 484 F. Supp. 2d 289 (E.D. Pa. 2007) (thimerosal); *Jackson v. Pfizer*, 432 F. Supp. 2d 964 (D. Neb. 2006) (antidepressants Zoloft and Effexor); *Laisure-Radke v. Par Pharm., Inc.*, 426 F. Supp. 2d 1163 (W.D. Wash. 2006) (antidepressant fluoxetine).

These suits are so numerous, and manufacturers' potential liability is so large and unpredictable, that the commercial liability insurance market has all but disappeared for medications. Rochelle Chodock et al., *"Insuring" The Continued Solvency of Pharmaceutical Companies in the Face of Product Liability Class Actions*, 40 Tort Trial & Ins. Prac. L.J. 997, 1000 (2005). "[M]ost pharmaceutical companies have extreme difficulty obtaining basic insurance coverage in the traditional liability insurance market." *Id.* Insurance experts have observed that "the pharmaceutical industry presents one of the most volatile risk management challenges in the world of business today." Mindy W. Toran, *Industry Risk Report: The Life Sciences*, Risk & Ins., Dec. 2003, at 1.

The growth in state-law tort suits challenging FDA-approved labeling has posed an increasingly serious threat to public health. As demonstrated below, patients may be deterred from using a needed medicine in the face of intimidating warnings that are driven by litigation rather than science. In addition, FDA's resources may be diverted to considering proposed labeling changes intended to reduce manufacturers' exposure to state-law tort liability. To the extent such changes are included in prescription drug labeling, they dilute the effectiveness of scientifically-justified warnings. In the most extreme instances, medicines that can save lives or cure disease have been withdrawn from the market or not brought to market at all.

C. State-Law Tort Suits Encourage Labeling Statements That Are Not Based on Science, Discouraging Physicians and Patients from Using Beneficial Medicines.

State-law tort suits challenging the adequacy of prescription drug labeling – and the publicity surrounding such suits – foster a proliferation of warnings about unsubstantiated risks that drive doctors and patients away from medicines that can improve health and save lives. FDA has long cautioned that "it would be inappropriate to require statements in drug labeling that do not contribute to the safe and effective use of the drug, but instead are intended solely to influence civil litigation in which the agency has no part." Content and Format for Labeling for Human Prescription Drugs, 44 Fed. Reg. 37,434, 37,435 (June 26, 1979). Yet as FDA observed in 2000, failure-to-warn suits have "caused manufacturers to . . . include virtually all known adverse event information, regardless of its importance or its plausible relationship to the drug." Requirements for Prescription Drug Product Labels, 65 Fed. Reg. 81,082, 81,083 (proposed Dec. 22, 2000).

The proliferation of inappropriate warnings harms patients in two ways. *First*, when labeling includes too many warnings, the warnings lose their effectiveness. As FDA has explained: "Overwarning has the effect of not warning at all. The reader stops paying attention to excess warnings." Center for Devices and Radiological Health, FDA, *Write it Right: Recommendations for Developing User*

Instruction Manuals for Medical Devices Used in Home Health Care 7 (1993). In a national survey, physicians criticized "the lack of ease in locating specific information among the extensive information presented" and labeling that "overly stresses the occurrence of extremely rare events." Requirements for Prescription Drug Product Labels, 65 Fed. Reg. at 81,083-84. In 2004, a bipartisan group of former FDA Chief Counsels stated that warnings required by state law erode "FDA's ability to advance the public health by allocating scarce space in product labeling to the most important information." 150 Cong. Rec. S8,657, S8,657 (July 22, 2004).[7]

Second, the inclusion of inappropriate warnings about speculative risks deters medicine use that may improve patients' health or save their lives. As the California Supreme Court observed in holding that federal law preempted a conflicting state-law warning requirement for an over-the-counter drug, "the risk of harm may be so remote that it is outweighed by the greater risk that a warning will scare consumers into foregoing use of a product that in most cases will be to their benefit." *Dowhal v. SmithKline Beecham Consumers Healthcare*, 88 P.3d

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[7] Plaintiff lawyers and other advocates now voice these same concerns, challenging warnings on the ground that they were "buried" among other warnings in the labeling, instead of being featured more prominently. *See, e.g.*, Public Citizen, Press Release, *Antibiotic Leads to Tendon Ruptures; FDA Ignores Risks* (Jan. 3, 2008) (criticizing antibiotic warning that was "far too easy to miss" given numerous other warnings surrounding it).

1, 14 (Cal. 2004). In some cases, the risk of harm is not only remote but non-existent.

These concerns are more than hypothetical. In October 2004, following an extended period of scientific discussion and media attention, FDA required pharmaceutical companies to add a "black box" warning suggesting that SSRI antidepressants may increase the risk of suicide in pediatric patients. During this period, from 2003 to 2005, SSRI prescriptions to those younger than age 15 declined by approximately 17 percent. Robert D. Gibbons, *Early Evidence on the Effects of Regulators' Suicidality Warnings on SSRI Prescriptions and Suicide in Children and Adolescents*, 164 Am. J. Psychiatry 1356, 1361 (2007). Between 2003 and 2004, "there was already a 14% increase in child adolescent suicide rates"—"the first increase of this magnitude in the child and adolescent suicide rate since the CDC began systematically collecting suicide data in 1979." *Id.* at 1358-59. As a result, the first systematic study of the effect of these new warnings concluded: "If the intent of the pediatric black box warning was to save lives, the warning failed, and in fact it may have had the opposite effect; more children and adolescents have committed suicide since it was introduced." *Id.* at 1361-62. The SSRI example involves FDA's exercise of its regulatory oversight; much greater harm can be expected from unsubstantiated warnings prompted by a deluge of state-law tort suits. Each of these lawsuits asks a jury to second-guess FDA's regulatory decisions in the context of a single patient, without giving adequate consideration to

other patients (not before the court) who would have been harmed had they *not* received the drug. *See Riegel*, 128 S. Ct. at 1008.

D. State-Law Tort Suits Can Deprive Doctors and Patients of Critical Medicines, By Inhibiting Drug Development or Driving Beneficial Drugs from the Market.

FDA is "responsible for advancing the public health by helping to speed innovations that make medicines and foods more effective, safer, and more affordable; and helping the public get the accurate, science-based information they need to use medicines and foods to improve their health." http://www.fda.gov/opacom/morechoices/mission.html (FDA Mission Statement) (last visited May 30, 2008); *see also* 21 U.S.C. § 393(b). In fulfilling its responsibility to protect the public health, FDA works to ensure that beneficial medicines are available to patients who need them.[8]

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[8] *See, e.g.*, 21 U.S.C. §§ 360aa-360dd (providing incentives for research, development, and marketing of drugs for treatment of rare diseases, for which costs may otherwise exceed expected profits); 21 C.F.R. §§ 316.1-316.52 (same); 21 U.S.C. § 356(a)(1) (FDA may "facilitate the development and expedite the review of [a new] drug if it is intended for the treatment of a serious or life-threatening condition and it demonstrates the potential to address unmet medical needs for such a condition"); 21 C.F.R. §§ 314.500-314.560 (same); 21 U.S.C. § 360bbb(b) (providing for patient use of investigational drugs if, among other requirements, there is "no comparable or satisfactory alternative therapy available to diagnose, monitor, or treat the disease or condition involved"); 21 C.F.R. § 312.34 (same).

Product-liability litigation challenging FDA-approved labeling can frustrate FDA's efforts to strike a balance that protects patient safety while securing the availability of needed medicines. As far back as 1988, the American Medical Association warned that "[p]roduct liability is having a profound negative impact on the development of new medical technologies." Adam R. Nelson, Amer. Med. Ass'n Bd. of Trustees, *Impact of Product Liability on the Development of New Medical Technologies* 1 (1988). In 1990, a study by the National Academy of Sciences concluded that "the net effect of the surge in liability costs has been to discourage innovation in the pharmaceutical industry." W. Kip Viscusi et al., *A Statistical Profile of Pharmaceutical Industry Liability, 1976-1989*, 24 Seton Hall L. Rev. 1418, 1419 (1994). In 1997, a peer-reviewed empirical study found that "a substantial premium exists in the U.S. pharmaceutical prices, strongly related to the prospective costs of litigation, which is absent in Canadian prices." Richard L. Manning, *Products Liability and Prescription Drug Prices in Canada and the United States*, 40 J.L. & Econ. 203, 227 (1997).

In some cases, litigation risk can drive valuable medicines entirely from the market, even when scientific research ultimately discredits the basis for the lawsuits. This is so in part because, "when a person using a prescription drug suffers a stroke or develops cancer, or her child has a birth defect, it can be quite unclear whether the injury is causally connected to use of a drug." Steven Garber, RAND, *Product Liability and the Economics of*

Pharmaceuticals and Medical Devices 46 (1993). Prescription drugs are often blamed for injuries that the patient would have suffered whether or not the patient had taken the drug. And unlike FDA scientists, jurors typically lack the medical and technical expertise to distinguish causal relationships from mere coincidence, let alone to evaluate the "complex chemical and pharmacological considerations" that go into determining whether a drug is safe and effective. *Weinberger v. Bentex Pharm., Inc.*, 412 U.S. 645, 654 (1973).[9]

Indeed, "products for patients with high rates of unexplained background injuries appear especially hazardous from a legal point of view." Garber, *supra*, at 63. As the following examples illustrate, state-law suits have the potential to drive from the market drugs that not only benefit many patients, but do not harm the plaintiffs who filed suit.

Vaccines. Experts have long asserted that second-guessing of FDA decisions has resulted in a mass exodus from the market for vaccines. "[S]ingle-product monopolies supply many of the vaccines for

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[9] Empirical research has shown that, when evaluating risk, "the typical juror appears to be subject to a massive hindsight bias." Reid Hastie & W. Kip Viscusi, *What Juries Can't Do Well: The Jury's Performance as Risk Manager*, 40 Ariz. L. Rev. 901, 917 (1998). In addition, research has demonstrated that juries are influenced by the severity of the plaintiff's injuries: the more seriously injured the plaintiff, the more likely the jury is to find that the defendant caused the injury. *See, e.g.*, Dennis J. Devine et al., *Jury Decision Making*, 7 Psychol. Pub. Pol'y & L. 622, 699 (2001).

major illnesses, including polio, measles, rabies, mumps, and rubella." W. Kip Viscusi, *Corporate Risk Analysis: A Reckless Act?*, 52 Stan. L. Rev. 547, 583 (2000). Vaccine shortages persist despite the National Vaccine Injury Compensation Program established in 1986 by Congress to minimize the burdens of state-law failure-to-warn suits. Plaintiffs can and do opt out of the federal program. *See, e.g.*, *Sykes v. Glaxo-SmithKline*, 484 F. Supp. 2d 289, 310 (E.D. Pa. 2007) (state-law suit alleging that plaintiff was harmed by thimerosal, a vaccine preservative, even though FDA had concluded that "[t]here is no evidence of harm from the use of thimerosal as a vaccine preservative") (quotations and alterations omitted).

Starting in the late 1970s, lawsuits alleged that pharmaceutical companies failed to warn that the whooping-cough component of the DPT vaccine caused permanent brain damage. Seven companies stopped making the vaccine; the lone company that continued to produce the vaccine lost a single state-law case and was subjected to a damages award equal to half the annual sales of the vaccine. To conserve vaccine supplies, the Centers for Disease Control and Prevention were forced to ask doctors "to stop vaccinating children over age one." Linda A. Willett, *Litigation as an Alternative to Regulation: Problems Created by Follow-On Lawsuits with Multiple Outcomes*, 18 Geo. J. Legal Ethics 1477, 1488 n. 60 (2005). Claims that the vaccine caused neurological harm were subsequently "discredited." Stephen D. Sugarman, *Cases in Vaccine Court –*

Legal Battles Over Vaccines and Autism, 357 N. Eng. J. Med. 1275, 1276 (2007).

There is evidence that the threat of litigation continues to inhibit development of a vaccine for AIDS. In 1986, the medical component of the National Academy of Sciences observed that, "[g]iven the extremely high cost of vaccine development programs and the present concerns over liability for vaccine-related injuries, many manufacturers may be unwilling to initiate or pursue the derivation or distribution of a vaccine to prevent AIDS." Institute of Medicine, National Academy of Sciences, *Confronting AIDS: Directions for Public Health, Health Care and Research* 222 (1986). One company "offered to donate to the U.S. government all the data its researchers ha[d] gathered over the years on the company's AIDS vaccine" and "request[ed] in exchange only that the government assume responsibility for any future liabilities." Charles Fenyvesi, *Shift and Shield*, U.S. News & World Report, June 15, 1992, at 24.

As the AIDS crisis continued into the 1990s, commercial liability insurance companies "den[ied] coverage to HIV vaccine researchers and manufacturers and experts predict[ed] that the unavailability of liability insurance [would] delay the marketing of any future FDA-approved vaccines." Kellen F. Cloney, *Note, AIDS Vaccine Manufacturers v. Tort Regime: The Need for Alternatives*, 49 Wash. & Lee L. Rev. 559, 570 (1992). Today, more than two decades after the first documented cases of AIDS, "[e]xposure to product liability lawsuits [remains] a

significant deterrent to [HIV] vaccine development in litigious environments such as the US." John Godwin, *HIV Treatments, Vaccines, and Microbicides: Toward Coordinated Advocacy*, Canadian HIV/AIDS Pol'y & L. Rev., Apr. 2004, at 1, 10.

Drugs for Pregnant Women. Pregnant women have also suffered as a result of lawsuits that ask juries to second-guess FDA determinations. In October 1979, "the National Enquirer published a story . . . linking Bendectin, a popular morning sickness drug, with birth defects." David E. Bernstein, *The Breast Implant Fiasco*, 87 Cal. L. Rev. 457, 460 (1999). After similar media reports, "suddenly thousands of claims had been filed" alleging that Bendectin caused birth defects in plaintiffs' children. *Id.* Questionable scientific theories drove the litigation, ultimately prompting this Court's landmark decision in *Daubert v. Merrell Dow Pharmaceuticals, Inc.*, 509 U.S. 579 (1993).[10]

Although the manufacturer prevailed in more than two-thirds of the trials, it nevertheless "withdrew Bendectin from the market, citing an increasing number of lawsuits and declining sales due to negative publicity." Joseph Sanders, *From Science to Evidence: The Testimony on Causation in*

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[10] Dubious science continues to find its way into state tort suits, because "only a minority of state courts have wholeheartedly adopted the *Daubert* trilogy." David E. Bernstein & Jeffrey D. Jackson, *The Daubert Trilogy in the States*, 44 Jurimetrics J. 351, 365 (2004).

the Bendectin Cases, 46 Stan. L. Rev. 1, 7 (1993). Subsequent "studies clearly demonstrate that Bendectin has no measurable reproductive risks to the mother or the fetus." Robert Brent, *Medical, Social, and Legal Implications of Treating Nausea and Vomiting of Pregnancy*, 186 Am. J. Obstetrics & Gynecology S262, S262-63 (2002).

The withdrawal of Bendectin increased health risks for pregnant women and babies. Without Bendectin, "hospital admission for morning sickness [has] doubled." Richard B. Stewart, *Regulatory Compliance as a Defense to Product Liability*, 88 Geo. L.J. 2167, 2171 (2000). The failure to treat severe morning sickness has an adverse effect on fetal nutrition and increases the risk of pregnancy complications. Brent, *supra*, at S264.

As the Bendectin example illustrates, liability risks would arise under state tort law even if a pregnancy drug were perfectly safe. That is so because "many pregnancies result in birth defects of unknown cause, and this leaves companies whose products were used during pregnancy vulnerable to suits." Garber, *supra*, at xxix. Indeed, "[w]ith over thirty million infants exposed to the product in utero, and a background rate of serious birth defects at perhaps 3 percent, ... [a]lmost one million babies born to mothers who used Bendectin would be expected to have had serious birth defects even if Bendectin had no such effect." *Id.* at 94-95.

Contraceptives. State-law tort litigation has also slowed contraceptive research. According to the

Institute of Medicine, "products liability litigation and the impact of that litigation on the cost and availability of liability insurance have contributed significantly to the climate of disincentives for the development of contraceptive products." Nat'l Research Council, Institute of Medicine, *Developing New Contraceptives: Obstacles and Opportunities* 141 (1990). For instance, liability costs drove the manufacturer to cease producing the Copper-7 contraceptive device – even though, at the time of withdrawal, the manufacturer had prevailed in nine of the eleven trials in which plaintiffs claimed that the device caused their injuries. *See* Garber, *supra*, at 93.

* * * *

Perversely, manufacturers' greatest liability risks tend to be associated with those patients who are most in need of beneficial medicines. For instance, "[w]ith a very substantial background rate of suicide among potential product users, the arithmetic of [antidepressants] is reminiscent of that of Bendectin." *Id.* at 99 (footnote omitted). Other essential products, used to treat common illnesses or classes of patients with high background rates of these illnesses, face the same problem. In these situations, in which the drug is crucial and the risk of a false positive is elevated, FDA's expertise is especially important.

II. Respondent's State-Law Tort Claims Are Preempted Under Well-Established Preemption Principles.

State law conflicts with federal law, and thus is preempted, when: (1) "compliance with both federal and state regulations is a physical impossibility," *Fla. Lime & Avocado Growers, Inc. v. Paul*, 373 U.S. 132, 142-43 (1963); or when (2) state law "stands as an obstacle to the accomplishment and execution of the full purposes and objectives of Congress," *Hines v. Davidowitz*, 312 U.S. 52, 67 (1941). Both types of conflict are present in this case. As the Vermont Supreme Court recognized, an "impossibility" conflict arises when adding warnings or instructions required by state law would violate federal law. Contrary to the Vermont court's decision, however, the scope of "impossibility" preemption in the pharmaceutical context is not limited to cases in which FDA has expressly rejected the precise warnings or instructions sought by the plaintiff. It also extends to cases – including this case – in which adding such language without prior FDA approval would violate federal law. This case also presents the "obstacle" type of conflict between state and federal law, because imposing liability under state tort law would alter FDA's careful balancing of the risks and benefits of prescription medications and cause FDA to be inundated with labeling supplements.[11]

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[11] A ruling for Petitioner in this case would not necessarily foreclose all state-law tort claims against manufacturers of prescription medicines. For example, this case does not involve

A. Respondent's State-Law Claims Are Preempted Because Adding The Instructions And Warnings At Issue Would Violate Federal Law.

1. There is no serious dispute that state law is preempted when it requires an action that is prohibited by federal law. As the Vermont Supreme Court acknowledged, if "FDA intended to prohibit defendant from strengthening the *Phenergan* label," then "it was impossible for defendant to comply with its obligations under both state and federal law." Pet. App. at 19a. *See also id.* at 17a (indicating that state-law claims would be preempted if FDA "would have rejected any attempt by [Petitioner] to strengthen its label").

Other courts agree that state law is preempted when it requires additional warnings or instructions that would violate federal law. For example, the Third Circuit recently held that federal law preempts state-law claims based on allegations that the manufacturers failed to warn of an association between antidepressants and suicide. *Colacicco v. Apotex, Inc.*, 521 F.3d 253 (3d Cir. 2008). In concluding that a suicide warning would have violated federal law, the court of appeals reasoned that "FDA has actively monitored the possible association between SSRIs and suicide for nearly twenty years, and has concluded that the suicide warnings desired by plaintiffs are without scientific

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material new safety information that was not reported to or considered by FDA.

basis and would therefore be false and misleading." *Id.* at 269. The Third Circuit reasoned that, "[b]ecause the standard for adding a warning to drug labeling is the existence of 'reasonable evidence of an association of a serious hazard with a drug,' and the FDCA authorizes the FDA to prohibit false or misleading labeling, a state-law obligation to include a warning asserting the existence of an association between SSRIs and suicidality directly conflicts with the FDA's oft-repeated conclusion that the evidence did not support such an association." *Id.* at 271 (citation omitted).

Likewise, the California Supreme Court, in a decision involving an over-the-counter drug, held that federal law preempted a state-law requirement that the manufacturer of a nicotine patch warn consumers that the patch was "not for use by pregnant women" and that the product "contains nicotine, a chemical known to the state of California to cause reproductive harm." *Dowhal*, 88 P.3d at 3-4. Again, the court concluded that the warning required by state law was prohibited by federal law: "FDA had rejected plaintiff's claim that his data justify a different warning, and defendants d[id] not claim to have any additional data." *Id.* at 9. Other courts have also recognized that, at a minimum, preemption is required when FDA has expressly rejected the scientific basis for the proposed warning underlying the plaintiff's failure-to-warn claim.[12]

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[12] *See, e.g., Horne v. Novartis*, 541 F. Supp. 2d 768, 2008 WL 818819, at *11 (W.D.N.C. 2008); *Sykes*, 484 F. Supp. 2d at 310; *Needleman v. Pfizer Inc.*, No. Civ. A. 3:03-CV-3074N, 2004 WL

These decisions are plainly correct. A different preemption rule would subject manufacturers to a Catch-22: If they changed the labeling they would violate federal law; if they did not change the labeling they could be held liable – repeatedly – under state law and could not adjust their conduct by modifying the labeling.

2. Although the Vermont Supreme Court correctly recognized that state-law tort claims are preempted when it is impossible to comply with both federal and state law, the court defined the scope of the "impossibility" conflict too narrowly. The Vermont court erroneously concluded that it was possible for Petitioner to comply with both federal and state law in this case because federal law "allows, and arguably encourages, manufacturers to add and strengthen" FDA-approved warnings without prior FDA approval. Pet. App. 11a. The Vermont Supreme Court's ruling rests on a misinterpretation of federal law.

The Vermont Supreme Court based its ruling on its interpretation of FDA's CBE regulation, 21 C.F.R. § 314.70(c). According to the Vermont court, this regulation grants manufacturers general permission to "add and strengthen warnings" without prior FDA approval. Pet. App. 11a. Contrary to the Vermont court's view, FDA has long interpreted its regulation as creating a limited exception that applies only to

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1773697, at *2 (N.D. Tex. Aug. 6, 2004); *Dusek v. Pfizer Inc.*, No. Civ. A H-02-3559, 2004 WL 2191804, at *6 (S.D. Tex. Feb. 20, 2004).

"concerns about *newly discovered* risks" and "important *new information* about the safe use of a drug." New Drug and Antibiotic Regulations, 47 Fed. Reg. at 46,623, 46,625 (emphasis added).[13] The agency's interpretation of the substantive meaning of its own regulation is entitled to substantial judicial deference. *See Auer v. Robbins*, 519 U.S. 452, 461 (1997).[14]

Correctly interpreted, Section 314.70(c) is a "narrow exception" to the general requirement that labeling, including labeling changes, must be approved in advance by FDA. Section 314.70(a)

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[13] In addition, no FDA approval is required for certain minor labeling changes, so long as the manufacturer informs the FDA of the changes in its next annual report to the agency. *See* 21 C.F.R. § 314.70(d)(2)(ix) (change "concerning the description of the drug product or in the information about how the drug product is supplied, that does not involve a change in the dosage strength or dosage form"); *id.* § 314.70(d)(2)(x) ("editorial or similar minor change").

[14] It is well-settled that "[f]ederal regulations have no less preemptive effect than federal statutes." *Fidelity Fed. Sav. & Loan Ass'n v. de la Cuesta*, 458 U.S. 141, 153 (1982). Moreover, an agency's determination that a state law poses an obstacle to achieving the purposes and objectives of federal law is also entitled to a degree of judicial deference. *See Medtronic, Inc. v. Lohr*, 518 U.S. 470, 496 (1996) ("agency is uniquely qualified to determine whether a particular form of state law stands as an obstacle to accomplishment and execution of the full purposes and objectives of Congress"); *Geier v. Am. Honda Motor Co.*, 529 U.S. 861, 883 (2000) (agency "likely to have a full understanding of its own regulation and objectives, and is uniquely qualified to comprehend the likely impact of state requirements").

applies only if the manufacturer has "newly acquired safety information," *i.e.*, information that has not previously been submitted to FDA and is not cumulative of previously-submitted information. Supplemental Applications, 73 Fed. Reg. at 2850.

In this case, there was no new newly-acquired information about Phenergan relevant to the risk at issue in this case. To the contrary, it is undisputed that FDA was fully aware of the risks of IV-push administration of Phenergan and had considered those risks over a period of decades. *See* Pet'r Br. 11-18. At the time Respondent was given Phenergan, the drug's labeling expressly warned that arterial injection may cause gangrene and require amputation. *See* Pet. App. 4a. Prior to Respondent's use of Phenergen, moreover, Petitioner sought to replace the existing warning with the following warning: "INJECTION THROUGH A PROPERLY RUNNING INTRAVENOUS INFUSION MAY ENHANCE THE POSSIBILITY OF DETECTING ARTERIAL PLACEMENT." *Id.* at 4a-5a. FDA rejected the proposed change and directed Petitioner to "[r]etain verbiage in current label." *Id.* at 162a.

At trial, Respondent argued, and the jury agreed, that "the label should not have allowed IV push as a means of administration." Pet. App. 3a. But there is no dispute that FDA had before it all available information regarding Phenergen when it approved the warning that allowed IV-push administration in limited circumstances. Because there was no new information about Phenergen relevant to the risk at issue in this case, Petitioner was not authorized to

change the labeling under Section 314.70(c), and thus making the labeling change sought by Respondent without prior FDA approval would have violated federal law.

In sum, there is substantial agreement that state-law tort claims against pharmaceutical manufacturers are preempted when it is impossible for manufacturers to comply with both federal and state law. The Vermont Supreme Court erred by failing to recognize that if Petitioner had made labeling changes to comply with state law it would have violated federal law. Accordingly, the state-law claims at issue in this case are preempted.

B. Respondent's State-Law Claims Are Preempted Because They Conflict With FDA's Balancing Of Risks And Benefits.

Respondent's state-law claims also conflict with federal law for a second reason: they pose a serious obstacle to FDA's careful balancing of the risks and benefits of prescription medicines. By allowing juries to second-guess FDA's balancing of risks and benefits, state law frustrates the objective of the FDCA and its implementing regulations, which is to promote the beneficial and safe use of medicines based on reasonable scientific evidence. The Vermont Supreme Court's contrary decision rests on a fundamental misunderstanding of the structure of

the FDCA and federal regulation of prescription drugs.[15]

A new drug application must include "the labeling proposed to be used for such drug." 21 U.S.C. § 355(b)(1)(F). When it approves a new drug, FDA exercises its exclusive authority under the FDCA to determine that the drug is safe and effective when used in accordance with the labeling and that the labeling is not "false or misleading in any particular." 21 U.S.C. § 355(d)(1), (2), (4), (5), (7). In making this judgment, FDA strikes a balance, as it did here, between the benefits and risks of the drug when so labeled. *See Rutherford*, 442 U.S. at 555 (FDA "generally considers a drug safe when the expected therapeutic gain justifies the risk entailed by its use.").

If FDA-approved warnings merely set a floor for additional regulation, then it would be open to States

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[15] The Vermont Supreme Court held that the 1962 amendments to the FDCA limit preemption under the FDCA to situations in which it is impossible to comply with both federal and state law. *See* Pet. App. 21a-23a (discussing Pub. L. No. 87-781, § 202, 76 Stat. 780, 793 (1962), which provides that "[n]othing in the amendments made by this act to the [FDCA] shall be construed as invalidating any provision of State law . . . unless there is a direct and positive conflict between such amendments and such provision of State law"). As Petitioner has explained, the Vermont court's interpretation of this statutory provision is incorrect. This Court's pre-1962 opinions repeatedly used the phrase "direct and positive conflict" to describe conflict preemption in general, including both "impossibility" and "obstacle" preemption. *See* Pet'r Br. 51-54 (collecting cases).

– through legislation, regulation, or common-law tort actions – to require additional warnings. Such warnings would alter FDA's risk-benefit determinations, and thus conflict with the federal agency's determination that the drug is safe and effective when used according to its FDA-approved labeling. For this reason, state-law claims are preempted where – as in this case – FDA has considered the risk at issue and decided whether and to what extent the drug's labeling should warn of that risk.

These basic preemption principles apply to state tort claims decided by juries just as they would apply to state statutes or administrative regulations that conflict with FDA's risk-benefit determination. As the Court recently observed in a related context, it is "implausible" to conclude that "a single state jury" has "greater power to set state standards 'different from, or in addition to' federal standards" than "state officials acting through state administrative or legislative lawmaking processes." *Riegel*, 128 S. Ct. at 1008 (quoting *Medtronic, Inc. v. Lohr*, 518 U.S. 470, 504 (Breyer, J., concurring)).[16]

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[16] This Court has recognized that the Supremacy Clause applies "beyond [states'] positive enactments, such as statutes and regulations, to embrace common-law duties." *Bates v. Dow AgroSciences LLC*, 544 U.S. 431, 443 (2005). *See also Riegel v. Medtronic, Inc.*, 128 S. Ct. 999, 1008 (2008); *Cipollone v. Liggett Group, Inc.*, 505 U.S. 504, 523 (1992). Although those cases involved express preemption provisions, the Court's reasoning applies equally to implied preemption: "[C]ommon-law liability is 'premised on the existence of a legal duty,' and a tort judgment therefore establishes that the defendant has violated

For all these reasons, jury verdicts in state-law pharmaceutical product liability cases frequently will conflict with FDA risk-benefit determinations reflected in a prescription drug's FDA-approved labeling. The conflict is greatly magnified when a potentially unlimited number of juries from 50 different states are asked to reach independent determinations about the appropriate balancing of risks and benefits. *See* J.A. 212 ("The FDA doesn't make the decision, you do."). These determinations can be expected to conflict with each other, as well as with FDA's determination. And because the consequences of an adverse jury verdict are so significant for the manufacturer, a relatively small number of adverse jury determinations may effectively displace FDA's risk-benefit determination.

To maintain FDA's careful balancing of risks and benefits, preemption analysis should not turn on whether FDA has disapproved the precise labeling language advocated by a particular plaintiff. Instead, the court should ask whether FDA has examined the relevant issue and approved warnings based on its review.

In this case, FDA reviewed the risks of administering Phenergan via IV push over a period of decades and approved a carefully calibrated set of

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a state-law obligation. . . . And while the common-law remedy is limited to damages, a liability award 'can be, and indeed is designed to be, a potent method of governing conduct and controlling policy.'" *Riegel*, 128 S. Ct. at 1008 (quoting *Cipollone*, 505 U.S. at 521-22).

warnings and instructions based on its balancing of risks and benefits. The risks and benefits of IV-push administration were well known, and Petitioner had no newly-acquired information that had not been submitted to FDA. Allowing individual juries to strike their own balance between the risks and benefits conflicts with the objectives of federal law, and thus is preempted.

C. Limiting Preemption to Cases In Which FDA Has Expressly Rejected Specific Labeling Language Will Cause FDA To Be Inundated With Labeling Applications.

The Vermont court's decision effectively conditions preemption on FDA's recitation of magic words. Although Petitioner had no new information about the risks of IV-push administration, Petitioner could have avoided liability in this case if it had asked FDA to expressly disapprove every possible permutation of instructions and warnings concerning IV-push administration.

If allowed to stand, the Vermont Supreme Court's decision will encourage manufacturers to inundate FDA with requests for labeling changes that FDA has already rejected in substance. To fend off labeling criticisms from plaintiffs and their experts, manufacturers will be encouraged to submit every conceivable labeling variation to FDA so as to come within the narrow scope of preemption recognized by the Vermont Supreme Court. Such a regime would place an excessive burden on FDA.

In a related FDA preemption context, the Court has already recognized that state tort claims may give manufacturers "an incentive to submit a deluge of information that the [FDA] neither wants nor needs, resulting in additional burdens on FDA's evaluation of an application," and delaying FDA action. *Buckman Co. v. Plaintiffs' Legal Comm.*, 531 U.S. 341, 351 (2001). After considering these burdens on FDA, the Court rejected the argument that the state-law claims at issue in *Buckman* would "affect only the litigants and [would] not have the kind of direct impact on the United States, which preemption is designed to protect from undue incursion." *Id.* at 351 n.6 (quotations omitted).[17]

Indeed, the burden on FDA that is created by the Vermont Supreme Court's approach to preemption is even more serious than the burden that concerned the Court in *Buckman*. Rather than dealing with the excess information as it sees fit, FDA is *required* to respond to labeling proposals.[18] An avalanche of additional labeling requests will distract FDA from

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[17] *See also, e.g., Mason v. SmithKline Beecham Corp.*, ___ F. Supp. 2d ___, 2008 WL 1835350, at *8 n.5 (C.D. Ill. Apr. 23, 2008) (under *Buckman*, federal law preempts plaintiffs' claims to the extent they suggest manufacturer withheld studies from FDA); *Horne*, 2008 WL 818819, at *14 (same).

[18] *See* 5 U.S.C. § 555(e) (requiring agency to give notice of the denial in whole or part of a written application or petition); *see also* 21 C.F.R. § 314.70(b)(4) (authorizing applicant to request expedited review of a supplement "for public health reasons" or if a delay "would impose an extraordinary hardship on the applicant").

its core responsibility of evaluating drugs' safety and effectiveness. This burden would be imposed at the very time that Congress is attempting to *strengthen* FDA's oversight powers in order to further safeguard the public health. *See* Food and Drug Administration Amendments Act of 2007, Pub. L. No. 110-85, 121 Stat. 823, tit. IX (2007).

FDA reporting requirements already generate "a deluge of information." Catherine T. Struve, *The FDA and the Tort System: Postmarketing Surveillance, Compensation, and the Role of Litigation*, 5 Yale J. Health Pol'y, L. & Ethics 587, 604 (2005). By creating an incentive for manufacturers to inundate FDA with labeling proposals, the state-law claim in this case poses an obstacle to the achievement of the purposes of federal law.

CONCLUSION

The judgment of the Supreme Court of Vermont should be reversed.

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WYETH,

Petitioner,

v.

DIANA LEVINE,

Respondent.

On Writ of Certiorari to the Supreme Court of Vermont

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BRIEF OF PRODUCT LIABILITY ADVISORY COUNCIL, INC., AS *AMICUS CURIAE* IN SUPPORT OF PETITIONER

INTEREST OF THE *AMICUS CURIAE*

Product Liability Advisory Council, Inc. ("PLAC") is a non-profit association with 121 corporate members representing a broad cross-section of American and international product manufacturers. These companies seek to contribute to the improvement and reform of the law in the United States and elsewhere, with an emphasis on the law governing the liability of manufacturers of products. PLAC's perspective is derived from the experiences of a corporate membership that spans a diverse group of industries in various facets of the manufacturing sector. Since 1983, PLAC has filed over 825 briefs as *amicus curiae* in both state and federal courts, including this Court, presenting the broad perspective of product manufacturers seeking fairness and balance in the application and development of the law as it affects product liability. A list of PLAC's corporate members is attached as Appendix A.[1]

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[1] Petitioner has filed a letter giving blanket consent to the filing of *amicus* briefs in this case; respondent's letter consenting to the filing of this brief has been filed with the clerk. No counsel for a party authored this brief in whole or in part, and no counsel or party made a monetary contribution intended to fund the preparation or submission of this brief. No person other than *amicus curiae*, its members, or its counsel made a monetary contribution to the preparation or submission of this brief.

PLAC—which filed *amicus* briefs in prior preemption cases including *Geier* v. *American Honda Motor Co.*, 529 U.S. 861 (2000), and *United States* v. *Locke*, 529 U.S. 89 (2000)—is well situated to address the issue of preemption raised in this case. PLAC's members are engaged in commerce in each of the 50 states and are subject in varying degrees to a wide range of federal regulations. Consequently, PLAC's members have often confronted the interplay between the duties imposed by federal law and the state common-law standards applied in product liability cases. Therefore, PLAC not only is uniquely suited to offer a broader perspective on preemption than the parties may provide, but it also is keenly interested in ensuring that the regulatory environment in which its members operate is a rational and consistent one.

INTRODUCTION AND SUMMARY OF ARGUMENT

The time has come for this Court to clarify once and for all that—contrary to the opinion below—the presumption against preemption simply does not apply to the analysis of whether state law conflicts with federal law. Although this Court has at times invoked the presumption when analyzing claims of *field* preemption and *express* preemption (albeit inconsistently and controversially), it almost never has done so when addressing claims of *conflict* preemption. Moreover, in recent decisions involving conflict preemption, the Court—by emphasizing ordinary principles of statutory interpretation and the inapplicability of any additional burdens prior to a finding of preemption—has clearly, albeit implicitly, signaled that the presumption indeed has

no role in conflict preemption analysis. It is time to make the implicit explicit.

Foundational and long-recognized principles of constitutional law and statutory construction fully justify not applying the presumption when engaging in conflict preemption analysis. As a preliminary matter, there is no textual basis in the Constitution for applying such a presumption in any circumstance, and, although never addressed by the Court, there are serious problems with the "federalism concerns" that have been invoked to justify the presumption. Furthermore, conflict preemption is fundamentally different from field and express preemption—the strands of preemption doctrine in which the Court traditionally has applied the presumption—in that conflict preemption analysis does not require a court to infer Congress's preemptive intent. Determining whether there is an actual conflict between state and federal law instead requires a judicial interpretation of the substantive—as opposed to the preemptive—meaning of a statute. As this Court's decisions indicate, such substantive interpretation does not implicate the presumption. Once an actual conflict has been identified as a matter of substantive law, a finding of preemption follows inescapably from the Supremacy Clause.

The Vermont Supreme Court, influenced by its mistaken application of the presumption against preemption, erroneously concluded that respondent's state-law tort claims do not conflict with federal law. Although this case arises in the context of federal drug regulation, its significance extends far beyond the pharmaceutical industry. If the decision below is allowed to stand, all manufacturers of federally

regulated products will be at risk of having to choose between complying with federal law or complying with state law. If they decide to comply with federal law, they will—like petitioner in this case—be exposed to multimillion dollar state-law tort liability. No company should be forced to make that choice or to suffer those consequences.

In addition to being fundamentally unfair, the decision below impedes interstate commerce and threatens the proper functioning of the federal regulatory system. In allowing private litigants to hold manufacturers liable under state law for failing to include risk warnings that are contrary to those mandated by the Food and Drug Administration, the Vermont Supreme Court—expressly disregarding the agency's views—misconstrued federal statute and misapplied this Court's precedent. In particular, the Vermont Supreme Court misinterpreted the meaning of a savings clause and disregarded this Court's teachings on the scope of conflict preemption. The results—both direct and indirect—are potentially devastating. Permitting juries in individual cases to substitute their *ad hoc* conclusions for those reached by an expert federal agency can easily upset the delicate regulatory balance struck by that agency after comprehensive review and careful consideration of all available scientific information. By undermining the Supremacy Clause, the decision below not only thwarts federal pharmaceutical policy, but threatens the efficacy of federal policy in other, similarly regulated industries.

ARGUMENT

I. The Presumption Against Preemption Is Inapplicable To Conflict Preemption Analysis.

This Court's recent case law, as well as established principles of constitutional law and statutory construction, provide strong grounds for concluding that the presumption against preemption has no application in the judicial determination of whether preemption is necessary because of an "actual conflict" between state and federal law. *Geier* v. *Am. Honda Motor Co.*, 529 U.S. 861, 884 (2000).[2] Accordingly, the Court should end years of ambiguity and avoidance of this question and clarify that a court may not invoke the presumption when analyzing claims of conflict preemption.

A. This Court's recent decisions indicate that the presumption against preemption does not apply to conflict preemption analysis.

As a general matter, the Court's adherence to the presumption against preemption—usually described as a requirement that Congress make its preemptive intent "clear and manifest" "[i]n areas of traditional state regulation," *Bates* v. *Dow Agrosciences LLC*, 544 U.S. 431, 449 (2005) (internal quotation marks omitted); see also *Medtronic, Inc.* v. *Lohr*, 518 U.S.

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[2] An "actual conflict" exists (i) where it is impossible for a private party to comply with both state and federal requirements, or (ii) where state law stands as an obstacle to the accomplishment of the full purposes and objectives of Congress. See, *e.g.*, *English* v. *Gen. Elec. Co.*, 496 U.S. 72, 79 (1990).

470, 485 (1996)—has been inconsistent and controversial. The Court's earliest Supremacy Clause cases made no mention of such a presumption. See, *e.g.*, *Martin* v. *Hunter's Lessee*, 14 U.S. (1 Wheat.) 304, 343–344 (1816); *Ware* v. *Hylton*, 3 U.S. (3 Dall.) 199 (1796) (applying no presumption in case where treaty superseded state criminal law). On the contrary, the Court recognized that "the acts of [a State] must yield to the law of Congress" even when the state law in question was "enacted in execution of acknowledged State power." *Gibbons* v. *Ogden*, 22 U.S. (9 Wheat.) 1, 210–211 (1824). Indeed, during the first several decades of the 20th century the Court recognized a strong generalized presumption *in favor* of preemption. See Mary J. Davis, *Unmasking The Presumption in Favor of Preemption*, 53 S.C. L. REV. 967, 973–983 (2002).

It was not until 1947 that this Court first explicitly recognized the existence of an "assumption" that the "historic police powers of the States" are not superseded when "Congress legislate[s] * * * in [a] field which the States have traditionally occupied" unless Congress makes its intent to do so "clear and manifest." *Rice* v. *Santa Fe Elevator Corp.*, 331 U.S. 218, 230 (1947). See Stephen A. Gardbaum, *The Nature of Preemption*, 79 CORNELL L. REV. 767, 806–807 (1994). At issue in *Rice* was whether Congress had displaced all state law in a particular field. Since *Rice*, the Court has on occasion applied this assumption of nonpreemption (also characterized as the "presumption against preemption") when analyzing claims of "field"

preemption.[3] The Court also has applied the doctrine when interpreting express preemption provisions, see, *e.g.*, *Bates*, 544 U.S. at 449; *Lohr*, 518 U.S. at 485; *Cipollone* v. *Liggett Group, Inc.*, 505 U.S. 504, 518 (1992)—although the application of the presumption in that context has not been without controversy. See, *e.g.*, *Engine Mfrs. Ass'n* v. *S. Coast Air Quality Mgmt. Dist.*, 541 U.S. 246, 256 (2004) (noting that "not all Members of this Court agree" on the "application" of the "presumption against pre-emption") (internal quotation marks omitted).[4]

By contrast, the Court almost without exception has avoided reliance on the presumption when addressing claims of conflict preemption.[5] It is true

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[3] See, *e.g.*, *English*, 496 U.S. at 79; *Hillsborough County* v. *Automated Med. Labs., Inc.*, 471 U.S. 707, 716 (1985); but see *Silkwood* v. *Kerr-McGee Corp.*, 464 U.S. 238, 247 (1984) (field preemption analysis makes no mention of presumption).

[4] At least two members of the Court reject the presumption's applicability in interpreting the scope of express preemption provisions. See, *e.g.*, *Bates*, 544 U.S. at 457 (Thomas, J., concurring in the judgment in part and dissenting in part); *Cipollone*, 505 U.S. at 544 (Scalia, J., concurring in the judgment in part and dissenting in part); see also *Engine Mfrs. Ass'n*, 541 U.S. at 256.

[5] See, *e.g.*, *Sprietsma* v. *Mercury Marine*, 537 U.S. 51 (2002); *Geier*, 529 U.S. 861; *United States* v. *Locke*, 529 U.S. 89 (2000); *Crosby* v. *Nat'l Foreign Trade Council*, 530 U.S. 363 (2000); *Freightliner Corp.* v. *Myrick*, 514 U.S. 280 (1995); *Gade* v. *Nat'l Solid Wastes Mgmt. Ass'n*, 505 U.S. 88 (1992) (plurality); *La. Pub. Serv. Comm'n* v. *FCC*, 476 U.S. 355 (1986); *Wis. Dep't of Indus., Labor & Human Relations* v. *Gould Inc.*, 475 U.S. 282 (1986); *Allis-Chalmers Corp.* v. *Lueck*, 471 U.S. 202 (1985); *Brown* v. *Hotel & Rest. Employees & Bartenders Int'l Union Local 54*, 468 U.S. 491 (1984); *Capital Cities Cable, Inc.* v. *Crisp*, 467 U.S. 691 (1984).

that, in *Hillsborough County* v. *Automated Med. Labs., Inc.*, 471 U.S. 707 (1985), and *California* v. *ARC America Corp.*, 490 U.S. 93 (1989), the Court did preface its conflict preemption analysis with a nod to the presumption. See 471 U.S. at 715–716; 490 U.S. at 101. In neither case, however, did the Court rely on the presumption in the actual analysis itself.[6] Indeed, in *Crosby* v. *National Foreign Trade Council*, 530 U.S. 363 (2000), the Court expressly recognized that the applicability of the presumption in the conflict preemption context remained an open question. See *id.* at 374 n.8 ("We leave for another day a consideration in this context of a presumption against preemption.").

Although the Court has yet to address the issue directly, several recent decisions strongly suggest that the presumption has no relevance in conflict preemption cases.

The Court's most notable recent precedent bearing on this issue is *Geier*, in which the Court held that federal law—a safety standard promulgated under the National Traffic and Motor Vehicle Safety Act of 1966—preempted a state law tort action seeking to impose liability on an automobile manufacturer for failing to install an airbag. See 529 U.S. at 881. Although a state law duty requiring automobile manufacturers to install airbags could plausibly be characterized as a core example of "state police power regulations,"

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[6] At least two post-*Rice* decisions addressing claims of both conflict and field preemption pointedly invoked the presumption only with reference to their field preemption analyses. See, *e.g.*, *Int'l Paper Co.* v. *Ouellette*, 479 U.S. 481, 491 (1987); *Jones* v. *Rath Packing Co.*, 430 U.S. 519, 525 (1977).

Cipollone, 505 U.S. at 518, "in a field which the States have traditionally occupied," *Lohr*, 518 U.S. at 485 (internal quotation marks omitted), the *Geier* majority never even mentioned, let alone applied, any presumption against preemption. See *Geier*, 529 U.S. at 906–907 (Stevens, J., dissenting) ("the Court simply ignores the presumption [against preemption]"). Indeed, rather than apply a presumption against preemption, the *Geier* majority expressly *rejected* the dissent's suggestion that Congress's inclusion of a savings clause in the relevant statute imposed a "special burden" that had to be overcome before preemption could be found. *Id.* at 872–874.

Strongly implying that the presumption against preemption has no relevance to conflict preemption analysis, the *Geier* Court emphasized that it was applying "ordinary," "longstanding," and "experience-proved principles of conflict pre-emption." *Geier*, 529 U.S. at 874. Under these principles, the sole question is whether there is an "actual conflict" between state and federal law; if there is such a conflict, then preemption follows automatically by operation of the Supremacy Clause. *Id.* at 871–872; see also *id.* at 872 (allowing "common-law actions that 'actually conflict' with federal regulations" would thwart "congressionally mandated objectives that the Constitution, through the operation of ordinary pre-emption principles, seeks to protect").

Other recent decisions of the Court are consistent with *Geier*'s apparent rejection of the presumption in conflict preemption cases. For example, in *United States* v. *Locke*, 529 U.S. 89 (2000), the Court, speaking unanimously, termed the presumption "artificial" and declined to invoke it

when analyzing whether certain state regulations conflicted with federal law. *Id.* at 108. And in *Sprietsma* v. *Mercury Marine*, 537 U.S. 51 (2002), the Court made no mention of the presumption when holding that a state law duty to install a propeller guard on a boat motor did not conflict with, and thus was not preempted by, the Coast Guard's decision not to require such guards. See *id.* at 64–68.[7] Rather than rely on the presumption against preemption, the Court based its decision on the Coast Guard's failure to "convey an 'authoritative' message of a federal policy against propeller guards." *Id.* at 67. Absent a federal policy against propeller guards, the Court found, federal law was not "inconsistent with a tort verdict premised on a jury's finding that" a propeller guard was required under the circumstances of the case. *Ibid.* Indeed, echoing *Geier*'s reliance on "ordinary * * * principles of conflict pre-emption," 529 U.S. at 874, the *Sprietsma* Court acknowledged that preemption would have followed automatically had there been a conflict between a federal regulation and a state common-law claim. See *Sprietsma*, 537 U.S. at 65 ("Of course * * * pre-emption would occur."). Thus, although no decision has explicitly held that the presumption against preemption has no role in conflict preemption analysis, the Court's recent opinions have, in apparent recognition of its inapplicability,

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[7] Notably, the Court *did* by contrast allude to the presumption in its analysis (and rejection) of possible *field* preemption under the relevant federal statute. See *Sprietsma*, 537 U.S. at 69 (observing that the "structure and framework" of the federal statute "do not convey a 'clear and manifest' intent * * * to implicitly pre-empt all state common law relating to boat manufacture").

consistently analyzed conflict preemption claims without reference to the presumption.

B. Basic principles preclude application of the presumption against preemption in conflict preemption analysis.

The Court's persistent refusal in recent decisions to invoke the presumption against preemption when analyzing conflict preemption issues is fully consistent with basic principles of constitutional law and statutory construction.

1. Notably, there is no basis in the text of the Constitution for a presumption against preemption. When Congress legislates within the scope of its enumerated powers, the Supremacy Clause renders its enactments "the supreme Law of the Land," U.S. CONST. art. VI, cl. 2, and "invalidates" "'interfer[ing]'" or "'contrary'" state law. *Hillsborough County*, 471 U.S. at 712 (quoting *Gibbons*, 22 U.S. at 211 (Marshall, C.J.)). "[S]ince [the Court's] decision in *M'Culloch* v. *Maryland*, 17 U.S. (4 Wheat.) 316, 427 (1819), it has been settled that state law that conflicts with federal law is without effect." *Cipollone*, 505 U.S. at 516 (internal quotation marks omitted).

Against the backdrop of this well-established framework rooted in the text of the Constitution, the Court has characterized the presumption against preemption as justified by "federalism concerns" (*Lohr*, 518 U.S. at 485), saying it "assur[es] that the federal-state balance will not be disturbed unintentionally by Congress or unnecessarily by the courts." *Jones*, 430 U.S. at 525 (internal quotation marks and citation omitted); see also *Geier*, 529 U.S. at 907 (Stevens, J., dissenting) (presumption is

necessary to allow "the structural safeguards inherent in the normal operation of the legislative process [to] operate to defend state interests from undue infringement").

But this justification is not universally recognized even in the express preemption context. See, *e.g.*, *Cipollone*, 505 U.S. at 544 (Scalia, J.) ("Under the Supremacy Clause, [the Court's] job is to interpret Congress's decrees of pre-emption neither narrowly nor broadly, but in accordance with their apparent meaning.") (citation omitted). More generally, the Supremacy Clause would itself appear to have resolved the invoked "federalism concerns" by establishing an unambiguous and bright-line constitutional rule for how federal and state law are to relate. Indeed, the Court has reiterated that "[u]nder the Supremacy Clause * * * the relative importance to the State of its own law is not material when there is a conflict with a valid federal law, for any state law, however clearly within a State's acknowledged power, which interferes with or is contrary to federal law, must yield." *Felder* v. *Casey*, 487 U.S. 131, 138 (1988) (internal quotation marks omitted); see also *DeCanas* v. *Bica*, 424 U.S. 351, 357 (1976) ("even state regulation designed to protect vital state interests must give way to paramount federal legislation").[8] Accordingly, to the extent the

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[8] To the extent that the federalism justification for the presumption rests on emanations from the Tenth Amendment, it would appear to be at odds with the decision last Term in *Watters* v. *Wachovia Bank, N.A.*, 127 S. Ct. 1559 (2007), in which the Court squarely held that the Tenth Amendment "is not implicated" in the preemption analysis because "'if a power is delegated to Congress in the Constitution, the Tenth Amendment expressly disclaims any reservation of that power

Court "systematically favor[s] one result over another" by applying a presumption against preemption when analyzing preemption questions, it "risk[s] an illegitimate expansion of the judicial function" by "disrupt[ing] the constitutional division of power between federal and state governments, rewrit[ing] the laws enacted by Congress, or both." Viet D. Dinh, *Reassessing the Law of Preemption*, 88 GEO. L.J. 2085, 2092 (2000).

As a matter of constitutional history, moreover, there is "no significant support * * * for the conclusion that the [F]ramers intended any * * * presumption to be read into [the Supremacy Clause]." Marin R. Scordato, *Federal Preemption of State Tort Claims*, 35 U.C. DAVIS L. REV. 1, 30 (2001). This is unsurprising given that the Framers' purpose in adopting the Supremacy Clause was "to remedy one of the chief defects in the Articles of Confederation by instructing courts to resolve state-federal conflicts in favor of federal law." David Sloss, *Constitutional Remedies for Statutory Violations*, 89 IOWA L. REV. 355, 402 (2004).

Indeed, the text of the Supremacy Clause, which provides that federal law "shall be the supreme Law of the Land * * * any Thing in the Constitution or Laws of any State to the Contrary notwithstanding" (U.S. Const. art. VI, cl. 2), clearly indicates that the Framers specifically *rejected* a presumption against preemption. The concluding phrase—"any Thing in the Constitution or Laws of any State to the Contrary notwithstanding"—is what the Framers and other eighteenth century lawyers would refer to

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to the States.'" *Id.* at 1573 (quoting *New York* v. *United States*, 505 U.S. 144, 156 (1992)).

as a "*non obstante*" provision. Routinely "used in public and private instruments," such provisions were "intended to preclude, in advance, any interpretation contrary to certain declared objects or purposes." Black's Law Dictionary (6th ed. 1990). As recent historical scholarship explains, the *non obstante* provision was included in the Supremacy Clause to ensure that the presumption against implied repeal, a doctrine already well established by the 18th century, would not thwart the Framers' intent that federal law trump conflicting state law. See Caleb Nelson, *Preemption*, 86 VA. L. REV. 225 (2000). Absent the *non obstante* provision, judges might have been unduly reluctant to declare a state law preempted. "Applying the normal presumption against implied repeals, they might strain the federal law's meaning in order to harmonize it with state law" (*id.* at 255), and thereby frustrate the purpose of the Supremacy Clause. Inclusion of the *non obstante* provision made clear that the presumption against implied repeal should not be applied to protect state law that conflicted with federal law from preemption even when Congress did not expressly declare the relevant state law void.

> [T]he final part of the Supremacy Clause is a global *non obstante* provision. This provision established a rule of construction, telling courts not to apply the traditional presumption against implied repeals in determining whether federal law contradicts state law. Thus, even if a federal statute or treaty did not itself contain a *non obstante* provision, the Supremacy Clause told courts not to strain its meaning in order to harmonize it with state law. As Daniel Webster asserted in his argument in

> *Gibbons v. Ogden*, "[t]he presence or absence of a *non obstante* clause[] cannot affect the extent or operation of the act of Congress," because "[t]he laws of Congress need no *non obstante* clause."

Ibid. Thus, rather than support a presumption *against* preemption, the Constitution's text, if anything, supports a presumption *in favor* of preemption.

2. Despite these unresolved challenges to the presumption's theoretical foundations, the Court's decisions indicate that its invocation may be justified when a court must *infer* congressional intent to determine whether a particular federal statute is preemptive in a particular situation. See *Smiley* v. *Citibank (S.D.), N.A.*, 517 U.S. 735, 744 (1996) (presumption applicable in determining "whether a statute is pre-emptive").

Both express and field preemption analyses may require such an inference in the first instance. Express preemption analysis generally involves judicial interpretation of "explicit statutory language," *English* v. *Gen. Elec. Co.*, 496 U.S. 72, 79 (1990), to determine whether it supplies an "express statement of pre-emptive intent," *Geier*, 529 U.S. at 884, and, if so, to "identify the domain" that Congress "intended" to invalidate by that statement. *Lohr*, 518 U.S. at 484–485 (internal quotation marks omitted).[9] Likewise, courts in field preemption cases

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[9] In such cases, the presumption provides a rule of statutory construction. See, *e.g.*, *Bates*, 544 U.S. at 449 (presumption against preemption imposes "duty" on court "to accept the reading" of statutory preemption provisions "that disfavors preemption"); *Cipollone*, 505 U.S. at 518 ("we must construe

look to the "substantive provisions of the legislation," *Cipollone*, 505 U.S. at 517 (internal quotation marks omitted), when determining whether "Congress intends that federal law occupy a given field." *ARC Am. Corp.*, 490 U.S. at 100.[10]

As the Court has explained, however, "conflict pre-emption is different." *Geier*, 529 U.S. at 884. Conflict preemption does not depend on an inference of congressional intent. Rather, conflict preemption depends on whether a conflict between state and federal law "in fact exists." *Ibid.*[11]

Whether there is an "actual conflict" between a particular federal statute and state law is a "question of the substantive (as opposed to preemptive) *meaning* of [that] statute." *Smiley*, 517 U.S. at 744. Interpreting the federal statute's substantive meaning is an inquiry that "does not bring into play" the presumption against preemption. *Ibid.*[12] Application of a presumption against

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these provisions in light of the presumption against * * * pre-emption").

[10] See also *Hillsborough County*, 471 U.S. at 714 ("The question whether the regulation of an entire field has been reserved by the Federal Government is, essentially, a question of ascertaining the intent underlying the federal scheme.").

[11] See also *Ouellette*, 479 U.S. at 491 (distinguishing judicial "inference" of field preemption, which courts should not undertake "lightly," from situation in which state law "actually conflicts" with federal law) (internal quotation marks omitted).

[12] See also *Brown*, 468 U.S. at 503 ("Where, as here, the issue is one of an *asserted substantive conflict* with a federal enactment, then the relative importance to the State of its own law is not material") (emphasis added; internal quotation marks and alterations omitted); *Fid. Fed. Sav. & Loan Ass'n* v. *de la Cuesta*, 458 U.S. 141, 153 (1982) (holding that principles of

preemption "rooted in the concept of federalism," *Geier*, 529 U.S. at 907 (Stevens, J., dissenting), would be particularly inappropriate when courts interpret Congress's substantive enactments because "Congress's chosen level of deference to state interests" is already "reflected in the language that Congress enacts." Nelson, 86 VA. L. REV. at 302. Applying the presumption to interpret federal law narrowly so as to reduce the likelihood that a conflict will be found would in effect "give the political safeguards of federalism a kind of double weight." *Id.* at 300. Accordingly, in a number of cases presenting issues of conflict preemption, this Court instead has applied its standard interpretive methods to arrive at broad constructions of substantive statutory meaning.[13]

Interpreting statutory language to determine its substantive meaning is distinct from, and must not be "confuse[d]" with, inferring whether and to what extent Congress intended to legislate preemptively. *Smiley*, 517 U.S. at 744. It is only in connection with the latter inquiry—which is relevant solely in the express preemption and field preemption contexts—that the presumption against preemption even arguably has a role to play. There is therefore no

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conflict preemption are "not inapplicable * * * simply because [state law at issue] is a matter of special concern to the States").

[13] See, *e.g.*, *Watters*, 127 S. Ct. at 1567 ("We have 'interpreted grants of both enumerated and incidental "powers" to national banks as grants of authority not normally limited by, but rather ordinarily pre-empting, contrary state law.'") (quoting *Barnett Bank of Marion County, N. A.* v. *Nelson*, 517 U.S. 25, 32 (1996)); *Allied-Bruce Terminix Cos.* v. *Dobson*, 513 U.S. 265, 275 (1995) (adopting "broad interpretation" of substantive language determining coverage of Section 2 of the Arbitration Act despite preemptive effect on conflicting state law).

warrant for invoking the presumption, as the Vermont Supreme Court did (see Pet. App. 7a), when analyzing whether state and federal law are in actual conflict.

3. Of course, once a conflict has been identified as a matter of substantive law, the Supremacy Clause requires that "state law [be] nullified to the extent that it actually conflicts with federal law." *Hillsborough County*, 471 U.S. at 713. Indeed, "'[t]he relative importance to the State of its own law is not material when there is a conflict with a valid federal law,' for 'any state law, however clearly within a State's acknowledged power, which interferes with or is contrary to federal law, must yield.'" *Felder*, 487 U.S. at 138 (quoting *Free* v. *Bland*, 369 U.S. 663, 666 (1962)). Accord *Geier*, 529 U.S. at 873. If there is an actual conflict between federal and state law, then the preemption of state law "is inescapable and requires no inquiry into congressional design." *Fla. Lime & Avocado Growers, Inc.* v. *Paul*, 373 U.S. 132, 142–143 (1963).

* * * * *

There is no basis in this Court's precedents, foundational principles of constitutional law, or the structure of our federal system for a court to invoke a presumption against preemption when analyzing a claim of conflict preemption. Straightforward application of the Supremacy Clause, by contrast, is not only consonant with the Constitution's history and text, but facilitates the realization of Congress's objectives and affords private actors—particularly in regulated fields—an important measure of legal

certainty and predictability.[14] The "day" has come for the Court to "consider[]" the presumption in the conflict preemption context, *Crosby*, 530 U.S. at 374 n.8, and to hold that the presumption has no applicability there.

II. The Decision Below Thwarts Important Federal Policy By Erroneously Denying Preemptive Effect To The FDA's Approval Of Petitioner's Drug Label.

The FDA is the expert federal agency charged by Congress with ensuring that drugs are safe and effective. To that end, the Food, Drug and Cosmetic Act ("FDCA") mandates that drug manufacturers obtain FDA approval to market prescription drugs. The agency decides whether to approve a drug based "on a comprehensive scientific evaluation of the product's risks and benefits under the conditions of use prescribed, recommended, or suggested *in the labeling*." Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products, 71 Fed. Reg. 3922, 3934 (Jan. 24, 2006) ("Preemption Preamble") (emphasis added) (citing 21 U.S.C. § 355(d)). Indeed,

> [t]he *centerpiece* of risk management for prescription drugs generally is the labeling which reflects thorough FDA review of the pertinent scientific evidence and

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[14] See *Geier*, 529 U.S. at 874 (noting the "legal uncertainty," and consequent "inevitable systemwide costs," imposed by an unnecessarily "complicated" preemption analysis); cf. *Cent. Bank* v. *First Interstate Bank*, 511 U.S. 164, 188 (1994) (noting "undesirab[ility]" of judicial "decisions made on an ad hoc basis, offering little predictive value") (internal quotation marks omitted).

> communicates to health care practitioners the agency's formal, authoritative conclusions regarding the conditions under which the product can be used safely and effectively. FDA carefully controls the content of labeling for a prescription drug, because such *labeling is FDA's principal tool for educating health care professionals about the risks and benefits of the approved product to help ensure safe and effective use.*

Ibid. (emphasis added); see also *id.* at 3967–3969; New Drug and Antibiotic Regulations, 50 Fed. Reg. 7452, 7470 (Feb. 22, 1985) ("Drug labeling serves as the standard under which FDA determines whether a product is safe and effective."). By imposing state-law tort liability on a drug manufacturer for failure to warn of a drug's dangers, despite the manufacturer's compliance with FDA labeling directives, the decision below "threaten[s] FDA's statutorily prescribed role as the expert Federal agency responsible for evaluating and regulating drugs." 71 Fed. Reg. at 3935.

A. State-law failure-to-warn liability conflicts with the FDA's goals of preventing overwarning and patchwork regulation.

The FDA's overarching goal in regulating the warning labels of pharmaceuticals is to strike the right balance between providing sufficient information to drug users and providing too many, or the wrong kind of, warnings. "In setting standards for drug labeling, FDA seeks to encourage the optimal level of use in light of reasonable safety concerns, by requiring scientific evidence that establishes an association between a drug and a

particular hazard before warning of that association on a drug's labeling." Brief of the United States As *Amicus Curiae* In Support of Defendants-Appellees, at 17, *Colacicco* v. *Apotex Inc.*, 521 F.3d 253 (3d Cir. 2008) (No. 06-3107), 2006 WL 5691532 ("FDA *Colacicco* Br.") (citing 21 C.F.R. § 201.80(e)). To achieve that goal, "FDA considers not only complex clinical issues related to the use of the product in study populations, but also important and practical public health issues pertaining to use of the product in day-to-day clinical practice." 71 Fed. Reg. at 3968. Through careful consideration of these factors, "appropriate warnings are drafted that identify established risks while avoiding inadequately substantiated risks, the mention of which could improperly deter use of the drug and result in harm to patients who unnecessarily forego medication." FDA *Colacicco* Br., 2006 WL 5691532, at *6.

In the Preemption Preamble, the FDA emphasized how delicate and important this balance is, and how overwarning can harm patients and interfere with regulatory goals:

> Given the comprehensiveness of FDA regulation of drug safety, effectiveness, and labeling under the act, additional requirements for the disclosure of risk information are not necessarily more protective of patients. Instead, they can erode and disrupt the careful and truthful representation of benefits and risks that prescribers need to make appropriate judgments about drug use.

71 Fed. Reg. at 3935; *accord* FDA *Colacicco* Br., 2006 WL 5691532, at *16 ("In considering the agency's views on drug labeling, it is critical to understand

that, where warnings are concerned, more is not always better."). Among other dangers, "[e]xaggeration of risk could discourage appropriate use of a beneficial drug." 71 Fed. Reg. at 3935. Moreover, "labeling that includes theoretical hazards not well-grounded in scientific evidence can cause meaningful risk information to 'lose its significance.'" *Ibid.* (quoting 44 Fed. Reg. 37,434, 37,447 (June 26, 1979)). Thus, "State-law attempts to impose additional warnings can lead to labeling that does not accurately portray a product's risks, thereby potentially discouraging safe and effective use of approved products or encouraging inappropriate use and undermining the objectives of the act." *Ibid.*; see also, *e.g.*, Brief for *Amicus Curiae* the United States of America at 23–24, *Motus* v. *Pfizer, Inc.*, 358 F.3d 659 (9th Cir. 2004) (No. 02-55372), 2002 WL 32303084 (explaining that "[u]nder-utilization of a drug based on dissemination of scientifically unsubstantiated warnings, so as to deprive patients of beneficial, possibly lifesaving treatment, could well frustrate the purposes of federal regulation as much as over-utilization resulting from a failure to disclose a drug's scientifically demonstrable adverse effects").

The courts of appeals have acknowledged the wisdom of preserving FDA primacy in reviewing and approving labeling for products over which it has regulatory authority. When the Third Circuit held in *Horn* v. *Thoratec Corp.*, 376 F.3d 163 (3d Cir. 2004), that the FDA's pre-market approval process for medical devices preempts state common-law claims alleging defective design and manufacture, the court relied upon the agency's conclusion that "'State common law tort actions threaten the statutory framework for the regulation of medical devices,

particularly with regard to FDA's review and approval of product labeling.'" *Id.* at 178 (emphasis added) (quoting the Letter Brief of *Amicus Curiae* the United States of America, at 25, *Horn* v. *Thoratec Corp.*, 376 F.3d 163 (3d Cir. 2004) (No. 02-4597), 2004 WL 1143720). Similarly, in *Brooks* v. *Howmedica, Inc.*, 273 F.3d 785 (8th Cir. 2001) (en banc)—a failure-to-warn case involving the labeling of a medical device approved by the FDA—the Eighth Circuit identified

> a number of sound reasons why the FDA may prefer to limit warnings on product labels. Warnings about dangers with less basis in science or fewer hazards could take attention away from those that present confirmed, higher risks. A label with many varied warnings may not deliver the desired information to users. Space on product labeling material is also a factor, and the most effective labels are those with large, bold warnings and a simple design.

Id. at 796.

None of these concerns is likely, however, to motivate—or even be considered by—a jury that is asked to decide a state failure-to-warn claim. All that such a jury would be called upon to determine is whether the content of the defendant's label satisfied the defendant's state-law duty to warn of the *particular* risk allegedly encountered by the *particular* plaintiff. If the jury answers that question in the negative, liability is almost certain to attach, regardless of the potential impact that the addition of that warning might have on *other* warnings with respect to other risks or on *other* patients' ability or willingness to use the product.

This problem is exacerbated by the case-by-case process of common-law adjudication. Later judges or juries cannot reconsider outcomes reached in earlier cases. Thus, a trier of fact cannot deem unnecessary or inappropriate a warning added in response to an earlier verdict. Nor do judges and juries know how many warnings will be vying for limited reader attention.

That is precisely the role of the FDA. As the Eighth Circuit has emphasized, "[i]t would be difficult for a jury focused on a single case to take into account 'the cumulative, systemic effects' of a series of verdicts. In contrast, the FDA possesses a broader perspective." *Brooks*, 273 F.3d at 797 (quoting Richard B. Stewart, *Regulatory Compliance Preclusion of Tort Liability: Limiting the Dual-Track System*, 88 GEO. L.J. 2167, 2175 (2000)). Even where a judge or jury is aware of potential overwarning, it can do little to prevent the problem. *See* James A. Henderson, Jr. & Aaron D. Twerski, *Doctrinal Collapse in Products Liability: The Empty Shell of Failure to Warn*, 65 N.Y.U. L. REV. 265, 302 (1990). As this Court recently emphasized in a decision finding preemption in the medical device arena, "tort law[] applied by juries" produces distorted results because it fails to emulate the cost-benefit analysis that an expert agency would employ. *Riegel* v. *Medtronic, Inc.*, 128 S. Ct. 999, 1008 (2008) ("A jury, on the other hand, sees only the cost of a more dangerous design, and is not concerned with its benefits; the patients who reaped those benefits are not represented in court.").

In light of these widely recognized dangers, the FDA has reasonably determined that state-law "product liability lawsuits have directly threatened

the agency's ability to regulate manufacturer dissemination of risk information for prescription drugs in accordance with the act." 71 Fed. Reg. at 3934. As the agency summarized in the Preemption Preamble:

> State actions are not characterized by centralized expert evaluation of drug regulatory issues. Instead, they encourage, and in fact require, lay judges and juries to second-guess the assessment of benefits versus risks of a specific drug to the general public—the central role of FDA—sometimes on behalf of a single individual or group of individuals. That individualized reevaluation of the benefits and risks of a product can result in relief—including the threat of significant damage awards or penalties—that creates pressure on manufacturers to attempt to add warnings that FDA has neither approved nor found to be scientifically required. This could encourage manufacturers to propose "defensive labeling" to avoid State liability, which, if implemented, could result in scientifically unsubstantiated warnings and underutilization of beneficial treatments.

Id. at 3935. Only comprehensive, exclusive regulation by an expert agency, such as the FDA, can solve the problem of overwarning by permitting an overall evaluation of risk and a rational decision about what risks are sufficiently serious to warrant inclusion on a label, how those warnings should be phrased, and where they should be placed. This is especially true where, as here, the intended readership consists not of ordinary consumers, but,

under the learned-intermediary doctrine, trained physicians who make judgments based on scientific data and information.

In addition to the danger of overwarning created when states require warnings not approved by the FDA, state regulation via failure-to-warn claims clashes with "the need for national uniformity in product regulation." *Brooks*, 273 F.3d at 797. As the FDA has noted, if judgments under state law were allowed to trump the FDA's assessment of what may appear in drug advertisements, "the public undoubtedly would receive inconsistent information from region to region." *Amicus Curiae* Brief of the United States, at 5, *In re Paxil Litig.*, No. CV 01-07937, 2002 WL 31375497 (C.D. Cal. Oct. 18, 2002), 2001 WL 34883537.

This Court has likewise recognized in the context of another federal labeling regime—the Federal Cigarette Labeling and Advertising Act of 1965—that the national economy can be greatly burdened if manufacturers of a product sold around the country are subjected to "diverse, nonuniform, and confusing * * * labeling and advertising regulations." *Cipollone*, 505 U.S. at 514. Congress, in the legislative history of the Medical Device Amendments to the FDCA, observed that, "if a substantial number of differing requirements applicable to a medical device are imposed by jurisdictions other than the Federal government, interstate commerce would be unduly burdened." H.R. REP. NO. 853, 45 (1976) (quoted in *Brooks*, 273 F.3d at 797). For these reasons, it was reasonable for the FDA to conclude that,

> [i]f State authorities, including judges and juries applying State law, were permitted to reach conclusions about the safety and

> effectiveness information disseminated with respect to drugs for which FDA has already made a series of regulatory determinations based on its considerable institutional expertise and comprehensive statutory authority, the federal system for regulation of drugs would be disrupted.

71 Fed. Reg. at 3969. Indeed, allowing respondent's claims to proceed would not only risk burdening interstate commerce in prescription drugs, but would also set a precedent that could adversely affect other federally-regulated industries.

B. The decision below misconstrues the relevant FDA regulation.

The decision below—which expressly disregards the considered views of the FDA (see Pet. App. 26a)—rests on a fundamental misunderstanding of the relevant FDA regulation. According to the Vermont Supreme Court, plaintiff's failure-to-warn claim does not conflict "with the FDA's labeling requirements for Phenergan because defendant could have warned against IV-push administration without prior FDA approval, and because federal labeling requirements create a floor, not a ceiling, for state regulation." Pet. App. 6a. The Vermont Supreme Court's decision rests on these false premises.

In fact, Wyeth was not at liberty to change the Phenergan label after its approval by the FDA. As the dissenting opinion explains, the applicable "regulation does not allow manufacturers to simply reassess and draw different conclusions regarding the same risks and benefits already balanced by the FDA." Pet. App. 40a. Rather, that regulation, 21 C.F.R. § 314.70(c), permits a manufacturer to make a

provisional label change *only* if there is newly discovered evidence of a previously unknown or underappreciated risk. As the FDA articulated when proposing § 314.70(c), the rule is designed to "make available important *new* information about the safe use of a drug product." New Drug and Antibiotic Regulations, 47 Fed. Reg. 46622, 46635 (Oct. 19, 1982) (emphasis added); see also Supplemental Applications Proposing Labeling Changes for Approved Drugs, Biologics, and Medical Devices, 73 Fed. Reg. 2848, 2849 (Jan. 16, 2008) ("reaffirm[ing]" "the agency's longstanding view" that a drug manufacturer may provisionally change an FDA-approved label without prior agency approval "only to reflect newly acquired information" because "permitting a sponsor to rewrite the labeling for a product following FDA's approval of a product and its labeling would disrupt FDA's careful balancing of how the risks and benefits of the product should be communicated"). In this case, however, there was no new information. The risks associated with arterial blood exposure to Phenergan were fully known by the FDA when it approved the Phenergan label. Indeed, in 1997, at the conclusion of a multiyear administrative review of the Phenergan label, the FDA—with specific reference to the risk of "Inadvertent Intra-arterial Injection"—expressly directed Wyeth to "[r]etain [the] verbiage in [the] current label." Pet. App. 162a. Accordingly, Wyeth was not permitted to change the label without prior FDA approval.

As the FDA explained in the Preemption Preamble, the view (adopted by the court below) that "FDA labeling requirements represent a minimum safety standard" that may be augmented by more stringent state-law requirements is a

"misunderstanding" of the FDCA and the regulations promulgated thereunder. 71 Fed. Reg. at 3934. Because "[o]verwarning, just like underwarning, can similarly have a negative effect on patient safety and public health," requirements imposed by the FDA pursuant to the FDCA "establish both a 'floor' and a 'ceiling.'" *Id.* at 3935. Thus, contrary to the decision below, allowing state law to require an additional warning beyond those required by the FDA would "frustrate the agency's implementation of its statutory mandate." *Id.* at 3934.

It would, moreover, place manufacturers in an impossible position. If subject to state-law failure-to-warn claims, drug manufacturers would be forced to add every conceivable warning to their labels or else risk—as in this case—multimillion dollar tort liability. At the same time, however, because "the determination whether labeling revisions are necessary is, in the end, squarely and solely FDA's under the act" (71 Fed. Reg. at 3934), adding warnings to drug labels without FDA approval would expose manufacturers to administrative enforcement actions (and even criminal prosecution under 21 U.S.C. §§ 331, 333, 352).[15] In some cases,

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[15] Furthermore, in what can fairly be called a Catch-22, adding warnings in response to potential tort liability might even increase a manufacturer's vulnerability to tort claims. As one commentator has suggested, "[i]t seems to be only a matter of time before a plaintiff succeeds in bringing an inadequate warning claim premised on the argument that, although a completely accurate statement of the risk had been provided, the pertinent warning lacked sufficient prominence because it was lost among the clutter of too many other cautionary statements on the label." Lars Noah, *The Imperative to Warn: Disentangling the "Right to Know" From the "Need to Know" About Consumer Product Hazards*, 11 YALE J. ON REG. 293,

manufacturers might respond to this dilemma by withdrawing certain products from the market, thereby diminishing interstate commerce and depriving the public of drugs that the FDA had determined to be safe and effective.

III. The Decision Below Conflicts With This Court's Precedent.

The FDA's interpretation of the FDCA is clear: Because state-law failure-to-warn tort claims interfere with the agency's expert determinations as to the proper balance to be struck in drug labels, "FDA approval of labeling under the act * * * preempts conflicting or contrary State law." 71 Fed. Reg. at 3934.[16] In reaching the opposite conclusion, the Vermont Supreme Court acknowledged the FDA's position, but declined to give it any weight, holding that "the FDA's statement deserves no deference." Pet. App. 26a. The Vermont Supreme Court's failure to defer to the FDA's interpretation of the FDCA is contrary to this Court's precedent.

A. The decision below conflicts with this Court's decisions concerning the deference due executive agencies.

Under the Supremacy Clause, Congress may of course preempt state statutory or common law through federal legislation. See U.S. CONST. art. VI, cl. 2; *Chicago & Nw. Transp. Co.* v. *Kalo Brick & Tile Co.*, 450 U.S. 311, 326–327 (1981). It is also well

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379–380 (1994); see also *id.* at 380 n.435 (describing similar cases in various contexts).

[16] This clear statement is the sort of "'authoritative' message of * * * federal policy" that the *Sprietsma* Court found lacking when it concluded that the state-law claims in that case were not preempted. 537 U.S. at 67.

settled that federal regulations implementing such statutes "have no less pre-emptive effect than federal statutes" themselves. *Fid. Fed. Sav. & Loan Ass'n* v. *de la Cuesta*, 458 U.S. 141, 153 (1982).

In the course of delineating the circumstances in which preemption occurs, this Court has held that a federal statute or regulation impliedly preempts any state law (including any state common law) that would "prevent or frustrate the accomplishment of a federal objective." *Geier*, 529 U.S. at 873–874; see also *Locke*, 529 U.S. at 109 (preemption is implied "when the state law stands as an obstacle to the accomplishment and execution of the full purposes and objective of Congress") (internal quotation marks omitted). When, as in the case of the FDA, Congress has delegated authority to an expert federal agency to implement and enforce a federal regulatory scheme, the agency's determination that state law threatens to upset federal objectives "is dispositive * * * unless either the agency's position is inconsistent with clearly expressed congressional intent, or subsequent developments reveal a change in that position." *Hillsborough County*, 471 U.S. at 714–715.

In this instance, the FDA is, pursuant to the FDCA, "the expert Federal agency responsible for evaluating and regulating drugs." 71 Fed. Reg. at 3935. See also 21 U.S.C. § 393(b)(2)(B) (the FDA is to ensure that "human * * * drugs are safe and effective"). As such, it has adopted—in the Preemption Preamble and numerous *amicus* briefs—an authoritative interpretation of the FDCA and the agency's own regulations according to which "FDA approval of labeling under the act * * * preempts conflicting or contrary State law." 71 Fed. Reg. at

3934. That determination—based on the agency's recognition that state-law failure-to-warn claims interfere with its ability to implement finely calibrated labeling decisions under the FDCA—is reasonable and entitled to full deference. "Because the FDA is the federal agency to which Congress has delegated its authority to implement the provisions of the Act, the agency is uniquely qualified to determine whether a particular form of state law 'stands as an obstacle to the accomplishment and execution of the full purposes and objectives of Congress,' and, therefore, whether it should be preempted." *Lohr*, 518 U.S. at 496 (citation omitted).

The fact that the FDA has articulated its preemption determination in a regulatory preamble and a series of *amicus* briefs does not diminish the deference owed that determination. As this Court has recognized, an agency's conclusion that federal law preempts state law may properly be communicated in "regulations, *preambles*, interpretive statements and responses to comments." *Hillsborough County*, 471 U.S. at 718 (emphasis added). Similarly, the fact that the "agency's fair and considered judgment on the matter in question" is conveyed "in the form of a legal brief" does not make the agency's view "unworthy of deference." *Auer* v. *Robbins*, 519 U.S. 452, 462 (1997). See also *Geier*, 529 U.S. at 883 (deferring to agency interpretation of ambiguous regulation contained in *amicus* brief submitted in dispute between private parties).

It was, therefore, contrary to this Court's precedent for the Vermont Supreme Court to disregard the FDA's authoritative determination that FDA approval of a drug label preempts state-law tort claims premised on the manufacturer's

failure to provide a warning not required by the FDA.

B. The decision below conflicts with this Court's decisions concerning the effect of savings clauses on implied preemption.

The Vermont Supreme Court's erroneous refusal to defer to the FDA's interpretation of the FDCA rests, in part, on that court's misunderstanding of this Court's preemption jurisprudence.

Recognizing that "deference to an agency's interpretation is appropriate only when a statute is 'silent or ambiguous with respect to the specific issue' the agency has considered," Pet. App. 25a (quoting *Chevron U.S.A., Inc.* v. *Natural Resources Defense Council, Inc.*, 467 U.S. 837, 842–843 (1984)), the Vermont Supreme Court disregarded the FDA's interpretation of the FDCA because, in that court's opinion, (a) drug manufacturers can add warnings required by state common-law standards on their own initiative without violating federal regulations, and (b) Congress, in a savings clause, expressly limited implied preemption in the drug context to situations in which compliance with federal and state law is a physical impossibility. See Pet. App. 21a, 26a–28a. But neither premise is correct. The first rests on the court's misunderstanding of 21 C.F.R. § 314.70(c), which—as discussed above—does *not* give drug manufacturers the power to add warnings unilaterally absent new, scientifically valid information. See pages 27–28, *supra*. The second rests on the court's misinterpretation of this Court's implied preemption doctrine.

Section 202 of the 1962 amendments to the FDCA provides that "[n]othing in the amendments

made by this Act * * * shall be construed as invalidating any provision of State law * * * unless there is a direct and positive conflict between such amendments and such provision of State law." Drug Amendments of 1962 § 202, Pub. L. 87-781, 76 Stat. 780, 793 (1962). In the view of the Vermont Supreme Court, this provision "remove[d] from [its] consideration the question of whether common-law tort claims present an obstacle to the purposes and objectives of Congress." Pet. App. 21a. That conclusion, however, is contrary to this Court's precedent.

As this Court made clear in *Geier*, a "saving clause * * * does *not* bar the ordinary working of conflict pre-emption principles." 529 U.S. at 869. Under those well established principles, "'conflicts' that prevent or frustrate the accomplishment of a federal objective and 'conflicts' that make it 'impossible' for private parties to comply with both state and federal law" are equally repugnant to the Supremacy Clause. *Id.* at 873. Accordingly, this Court has steadfastly "refused to read general 'saving' provisions"—such as Section 202—"to tolerate actual conflict *both* in cases involving impossibility *and* in 'frustration-of-purpose' cases." *Id.* at 874 (citations omitted). Because any form of conflict between federal and state law is intolerable to the Supremacy Clause, this Court rejects "attempting to distinguish among types of federal-state conflict for purposes of analyzing whether such a conflict warrants pre-emption in a particular case." *Ibid.*

That, however, is precisely what the Vermont Supreme Court did. It interpreted Section 202 as abrogating state law only when simultaneous

compliance with federal law is impossible, but as preserving state law even if it "present[s] an obstacle to the purposes and objectives of Congress." Pet. App. 21a. Neither the Supremacy Clause nor this Court's precedent permits such a bizarre result.[17]

CONCLUSION

The judgment of the Vermont Supreme Court should be reversed.

Respectfully submitted.

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[17] Notably, the language used by Congress in Section 202 to describe which state laws are preempted—namely state laws that are in "direct and positive conflict" with federal law—is identical to that used by this Court in *Sinnot* v. *Davenport*, 63 U.S. (22 How.) 227, 243 (1859). In that case, this Court held that a state law, which imposed a registration requirement on steamboats beyond that imposed by a federal law meant to facilitate interstate transport, was preempted *even though simultaneous compliance with both state and federal law was not impossible*. Thus, *Sinnot* makes clear that the phrase "direct and positive conflict" encompasses situations in which state law, although not physically incompatible with federal law, nonetheless impedes attainment of the federal statutory objective.

APPENDIX

APPENDIX A

Corporate Members of the Product Liability Advisory Council (as of May 12, 2008)

3M

ACCO Brands Corporation

Altec Industries

Altria Corporate Services, Inc.

American Suzuki Motor Corporation

Andersen Corporation

Anheuser-Busch Companies

Arai Helmet, Ltd.

Astec Industries

BASF Corporation

Bayer Corporation

Beretta U.S.A Corp.

BIC Corporation

Biro Manufacturing Company, Inc.

Black & Decker (U.S.) Inc.

BMW of North America, LLC

Boeing Company

Bombardier Recreational Products

BP America Inc.

Bridgestone Americas Holding, Inc.

Briggs & Stratton Corporation

Brown-Forman Corporation

CARQUEST Corporation

Caterpillar Inc.

Chrysler LLC

Continental Tire North America, Inc.

Cooper Tire and Rubber Company

Coors Brewing Company

Crown Equipment Corporation

Daimler Trucks North America LLC

The Dow Chemical Company

E.I. DuPont De Nemours and Company

Easton-Bell Sports, Inc.

Eaton Corporation

Eli Lilly and Company

Emerson Electric Co.

Engineered Controls International, Inc.

Estee Lauder Companies

Exxon Mobil Corporation

Ford Motor Company

Genentech, Inc.

General Electric Company

General Motors Corporation

GlaxoSmithKline

The Goodyear Tire & Rubber Company

Great Dane Limited Partnership

Harley-Davidson Motor Company

Hawker Beechcraft Corporation

The Heil Company

Honda North America, Inc.

Hyundai Motor America

Illinois Tool Works, Inc.

International Truck and Engine Corporation

Isuzu Motors America, Inc.

Jarden Corporation

Johnson & Johnson

Johnson Controls, Inc.

Joy Global Inc., Joy Mining Machinery

Kawasaki Motors Corp., U.S.A.

Kia Motors America, Inc.

Koch Industries

Kolcraft Enterprises, Inc.

Komatsu America Corp.

Kraft Foods North America, Inc.

Leviton Manufacturing Co., Inc.

Lincoln Electric Company

Magna International Inc.

Mazda (North America), Inc.

Medtronic, Inc.

Merck & Co., Inc.

Michelin North America, Inc.

Microsoft Corporation

Mine Safety Appliances Company

Mitsubishi Motors North America, Inc.

Mueller Water Products

Nintendo of America, Inc.

Niro Inc.

Nissan North America, Inc.

Nokia Inc.

Novartis Consumer Health, Inc.

Novartis Pharmaceuticals Corporation

Occidental Petroleum Corporation

PACCAR Inc.

Panasonic

Pfizer Inc.

Porsche Cars North America, Inc.

PPG Industries, Inc.

Purdue Pharma L.P.

Putsch GmbH & Co. KG

The Raymond Corporation

Remington Arms Company, Inc.

Rheem Manufacturing

RJ Reynolds Tobacco Company

Sanofi-Aventis

Schindler Elevator Corporation

SCM Group USA Inc.

Shell Oil Company
The Sherwin-Williams Company
Smith & Nephew, Inc.
St. Jude Medical, Inc.
Subaru of America, Inc.
Synthes (U.S.A.)
Terex Corporation
Textron, Inc.
TK Holdings Inc.
The Toro Company
Toshiba America Incorporated
Toyota Motor Sales, USA, Inc.
TRW Automotive
UST (U.S. Tobacco)
Vermeer Manufacturing Company
The Viking Corporation
Volkswagen of America, Inc.
Volvo Cars of North America, Inc.
Vulcan Materials Company
Watts Water Technologies, Inc.
Whirlpool Corporation
Wyeth
Yamaha Motor Corporation, U.S.A.
Yokohama Tire Corporation
Zimmer, Inc.

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No. 06-1249

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In the

Supreme Court of the United States

WYETH,

Petitioner,

v.

DIANA LEVINE,

Respondent.

On Writ of Certiorari to the Supreme Court of Vermont

BRIEF OF TORTS PROFESSORS MARK P. GERGEN AND MICHAEL D. GREEN AS *AMICI CURIAE* IN SUPPORT OF RESPONDENT

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August 14, 2008

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INTEREST OF THE *AMICI CURIAE*[1]

Amici are law professors who regularly teach and write about the law of torts. Each has taught for more than 20 years, has written extensively in the field, and has been a reporter for a segment of the *Restatement (Third) of Torts*. Further biographical information is included in the Appendix.

Amici have no stake in the outcome of this case other than their academic interest in the logical and rational development of the law. Because this case implicates fundamental issues of tort law, *amici* believe that their unique perspective may assist the Court in its resolution of this case.

SUMMARY OF THE ARGUMENT

Petitioner's policy arguments for preemption are unduly optimistic about the ability of the Food and Drug Administration ("FDA") to protect the public from unreasonably dangerous drugs. The civil system complements FDA regulation of drugs. Even if the agency were adequately funded and staffed, and even if drug makers always cooperated with the agency to ensure the safety and efficacy of drugs, tort liability would still be necessary to encourage drug makers to provide adequate warnings about risks that are outside the agency's purview when it approves a drug and labeling. Tort liability also serves compensation and corrective justice interests that FDA regulation was never intended to serve.

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[1] No counsel for a party authored this brief in whole or in part and no person other than *amici* and their counsel made a monetary contribution to fund its preparation or submission. The parties have consented to the filing of this brief.

Petitioner's policy arguments for preemption also assume an unduly pessimistic view of the civil justice system. Mechanisms already exist within the civil justice system to ensure courts and juries defer to FDA approval of drugs and labeling and to protect drug makers from spurious claims. State courts have struck a balance by adopting rules that shield a drug maker from design-defect claims while holding a drug maker liable if it fails to give adequate warning of a drug's risks. This facilitates getting new FDA-approved drugs on the market while using failure-to-warn liability to encourage dissemination of risk information and so enable health-care professionals and the public to make informed decisions about drugs. Other rules address specific arguments for preemption. Rules of evidence enable courts to screen out claims that lack a sound scientific basis. The hypothetical danger of drug makers' inundating the public with warnings to avoid liability is dealt with by the learned intermediary doctrine, which provides that a drug maker can satisfy the duty to warn by providing information to health-care professionals.

The American Law Institute ("ALI"), state courts, and state legislatures have directly grappled with the arguments for and against requiring courts and juries to defer to FDA approval of a drug's labeling in developing what has come to be called the defense of regulatory compliance. Many states have statutes that require courts and juries to give some deference to FDA approval of a drug's labeling. While it remains a minority position, there is some support for a rule that would shield a drug maker from liability for failure to warn if the FDA addressed the specific risk at issue in a case and determined additional

warning was unwarranted. These rules would not shield petitioner here because the FDA never approved the administration of Phenergan by IV-push. No court and only one state legislature, Michigan, has gone so far as to make FDA approval of a drug and its labeling a shield against claims involving risks that the FDA has not addressed.

This experience teaches that preemption is not an either-or proposition. A narrow rule of preemption is similar to a strong form of the common-law defense of regulatory compliance. This would treat FDA approval of the adequacy of a warning with regards to a specific risk as determinative of the issue of the reasonableness of the warning about this risk so long as the FDA considered all relevant information. Petitioner would not be satisfied with such a rule for it would not shield it from liability in this case. A broad rule would make the FDA solely responsible for ensuring the adequacy of warnings of FDA-approved drugs by precluding all failure-to-warn claims with respect to FDA-approved drugs. This would shield a drug maker from liability even if it withheld relevant risk information from the FDA or otherwise failed to cooperate, and even with respect to risks that appear post-marketing or that involve "off-label" uses, which the FDA has not had an opportunity to consider. This would be a radical change from the status quo. Only Michigan has gone this far. This Court should leave it to Congress to tailor an appropriate preemption rule and to decide whether the rule should apply retroactively or only prospectively.

ARGUMENT

I. Preemption of state-law tort claims based on FDA regulation of a drug is unwarranted because the civil justice system complements the FDA's regulation of drugs.

The civil justice system complements FDA regulation of drugs on two general dimensions. First, tort liability serves several important functions that FDA regulation of drugs was never intended to serve. Most of these functions involve compensating people who are injured, usually because a drug maker failed to provide adequate warning of a drug's risks. Whether the civil justice system should be preempted from serving these compensatory functions raises fundamental questions of morality and policy. Tort liability also complements the FDA's regulatory function. Whether the civil justice system should be preempted from serving this function turns on an assessment of the relative strengths and weaknesses of FDA regulation and of civil liability as mechanisms for protecting people from unreasonably dangerous drugs. At bottom, the answers to both questions turn on whether we as a society choose to err on the side of over- or under-protecting the public from unreasonably dangerous drugs. To date, state courts have struck a balance by eliminating barriers that might deter the introduction of new drugs, relying on the FDA to keep unreasonably dangerous drugs off the market, while imposing failure-to-warn liability to encourage dissemination of risk information and so enable health-care professionals and the public to make informed judgments about drugs.

Until the FDA's recent change in position, no official body, not even the agency, had concluded that

a general rule preempting failure-to-warn liability was needed to enable the agency to accomplish its mission.[2] The FDA announced a change in its views on the need for preemption in the preamble to the 2006 labeling regulations. Putting aside the question whether this was an appropriate way to make such an important change in policy, it is striking that this case is not within any of the categories of cases for which the agency itself deemed preemption to be necessary.[3]

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[2] There is explicit recognition of this in the 2000 proposed regulations on prescription drug labeling. The preamble stated: "FDA has determined that this proposed rule does not contain policies that have federalism implications or that preempt State law." 65 FED. REG. 81,082, 81,103 (Dec. 22, 2000).

[3] The preamble to the 2006 labeling regulations states, in pertinent part:

> FDA believes that at least the following claims would be preempted by its regulation of prescription drug labeling: (1) Claims that a drug sponsor breached an obligation to warn by failing to put in Highlights or otherwise emphasize any information the substance of which appears anywhere in the labeling; (2) claims that a drug sponsor breached an obligation to warn by failing to include in an advertisement any information the substance of which appears anywhere in the labeling, in those cases where a drug's sponsor has used Highlights consistently with FDA draft guidance regarding the "brief summary" in direct-to-consumer advertising . . . ; (3) claims that a sponsor breached an obligation to warn by failing to include contraindications or warnings that are not supported by evidence that meets the standards set forth in this rule, including § 201.57(c)(5) (requiring that contraindications reflect "[k]nown hazards and not theoretical possibilities") and (c)(7); (4) claims that a drug sponsor breached an obligation to warn by failing to include a statement

A. Compensation and loss spreading.

By compensating individuals harmed by drugs, tort law serves some ends that FDA regulation simply is not meant to serve. Most importantly, "preemption completely eliminates the corrective justice role that common law courts have played in this country since its founding." THOMAS O. MCGARITY, THE PREEMPTION WAR 33 (Yale 2008). For much of this country's history, the purpose of tort law was thought to be redressing moral wrongs, not regulation or deterrence. In the last half century in the United States, tort law has come to be understood as also serving a regulatory function. But corrective justice or compensation remains an important goal.

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in labeling or in advertising, the substance of which had been proposed to FDA for inclusion in labeling, if that statement was not required by FDA at the time plaintiff claims the sponsor had an obligation to warn (unless FDA has made a finding that the sponsor withheld material information relating to the proposed warning before plaintiff claims the sponsor had the obligation to warn); (5) claims that a drug sponsor breached an obligation to warn by failing to include in labeling or in advertising a statement the substance of which FDA has prohibited in labeling or advertising; and (6) claims that a drug's sponsor breached an obligation to plaintiff by making statements that FDA approved for inclusion in the drug's label (unless FDA has made a finding that the sponsor withheld material information relating to the statement).

71 FED. REG. 3922, 3935-36 (Jan. 24, 2006) (second alteration in original). The closest categories are (3), (4), and (5). The case is not within (3) because the risk of intravenous injection of Phenergan is well-established. It is not within (4) because a warning against administration of Phenergan by IV-push was never proposed to the FDA. It is not within (5) because the FDA never prohibited Wyeth from warning against administration of Phenergan by IV-push.

See *Warriner v. Stanton*, 475 F.3d 497, 501 (3d Cir. 2007) (reaffirming that New Jersey's tort policies consist primarily of compensation and deterrence); *Hannah v. Heeter*, 584 S.E.2d 560, 566 (W. Va. 2003) ("the three fundamentals of tort law are morality, compensation, and deterrence") (internal quotation marks omitted). See generally Gary T. Schwartz, *Mixed Theories of Tort Law: Affirming Both Deterrence and Corrective Justice*, 75 TEX. L. REV. 1801 (1997). In Europe, civil liability generally still is understood to serve corrective justice. For this reason, there has been almost no movement in Europe to eliminate civil liability for unreasonably dangerous products and to rely solely on administrative regulation of dangerous products.[4]

From the perspective of corrective justice, FDA approval of drug labeling is relevant only insofar as

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[4] In the European Union ("EU") there generally are two tiers of administrative approval, at the EU level and the member state level. The European Agency for the Evaluation of Medicinal Products ("EMEA"), which was established in 1995, must authorize marketing a drug within the EU. Most individual countries also require approval by their own agency, such as the Medicines and Healthcare Products Regulatory Agency ("MHRA") in the UK and the Federal Institute for Drugs and Medical Devices ("BfArM") in Germany. See CHRISTOPHER HODGES, EUROPEAN REGULATION OF CONSUMER PRODUCT SAFETY, Ch. 4 (Oxford 2004). An industry position paper has cited "a very low level of compensation claims" as evidence of the success of the administrative system. *Id.* at 43.

Section 4(1)(a) of the 1985 European Directive on Product Liability makes compliance with a regulation a defense. See SIMON WHITTAKER, LIABILITY FOR PRODUCTS 522 (Oxford 2005) ("This defence is not, of course, a defence of compliance with public standards (though such a defence has been suggested): it requires that the defect itself results from the regulatory standard.").

it establishes that a company did nothing morally blameworthy in not providing an additional warning. FDA approval of a label would be significant on this question if the FDA advised a drug maker that a particular warning was adequate with regards to the specific risk in question in a case (and it would be decisive if the FDA forbade the drug maker from providing an additional warning), but otherwise it is of no obvious relevance.

Compensation through strict liability also serves to spread losses. See, e.g., *New Texas Auto Auction Servs., LP v. Gomez De Hernandez*, 249 S.W.3d 400, 404 (Tex. 2008) (stating the justifications for strict liability are "(1) compensating injured consumers, (2) spreading potential losses, and (3) deterring future injuries"); *Antone v. Greater Arizona Auto Auction*, 155 P.3d 1074, 1076 (Ariz. Ct. App. 2007) ("[T]he underlying justification for imposing strict liability is risk/cost spreading to those parties in the distribution chain that are best able to both bear the cost and protect the consumer from defective products."), *review denied* (Ariz. Sept. 25, 2007). The loss-spreading justification is buttressed by the insight of law and economics that the cost of accidents is minimized by imposing the cost on "the 'cheapest cost avoider' or [the actor] who is in the best position to make the cost-benefit analysis between accident costs and accident avoidance costs and to act on that decision once it is made." *Beshada v. Johns-Manville Prods. Corp.*, 447 A.2d 539, 548 (N.J. 1982) (citing Guido Calabresi & Jon T. Hirschoff, *Toward a Test for Strict Liability in Torts*, 81 YALE L.J. 1055 (1972)). See generally Robert L. Rabin, *Reassessing Regulatory Compliance*, 88 GEO. L.J. 2049, 2071 (2000).

For a court or state legislature that held these views, a determination by the FDA that the cost of an additional warning outweighed the benefits would be beside the point, even if the lawmaker was confident the FDA was right. *Schneider Nat'l, Inc. v. Holland Hitch Co.*, 843 P.2d 561, 580 (Wyo. 1992) ("The risk allocation concept means that strict liability is not based on 'fault.' Instead of considering each actor's negligence or fault, the person most able to avoid accidents . . . is held liable for the cost of the accident.") (citations omitted). The court or legislature would still want to impose liability to spread losses from risks in a use of a drug that the FDA correctly determined were worth taking.[5] If the court or legislature thought there was a risk of regulatory error, then they would have an additional reason for imposing strict liability for it would increase their confidence that a company would warn of a risk if the benefits of the additional warning outweighed the cost.

In the United States, the trend in products liability law has been away from strict liability and towards negligence-based liability. This is particularly true in the area of pharmaceuticals with regards to

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[5] See *Wilson v. Piper Aircraft Corp.*, 577 P.2d 1322, 1333 (Or. 1978) (Linde, J., concurring) ("In a state where common law or legislation imposed absolute liability on a producer for certain kinds of harm in fact caused by his product, the fact that it had been thoroughly tested and approved for safety would be immaterial. But when liability is predicated on finding a design 'dangerously defective,' not 'duly safe,' or short of some similarly phrased standard of safety, then a careful comparison of that standard and the one attested to by the certificate becomes important.").

design defects.[6] See Jane Stapleton, *Liability for Drugs in the U.S. and EU: Rhetoric and Reality*, 26 REV. LITIG. 991 (2007).[7] But, as Professor Rabin has observed:

> More than a half century after *Escola [v. Coca Cola Bottling Co.*, 150 P.2d 436 (Cal. 1944)], the courts still have not reached a consensus on which rationale [compensation or regulation] should prevail. The divide is defined by those courts (and commentators) that would limit design defect and inadequate warning liability to some version of risk-benefit analysis, contrasted with those that would recognize a consumer expectations rationale, as well.

Rabin, 88 GEO. L.J. at 2071.

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[6] *Grundberg v. Upjohn Co.*, 813 P.2d 89 (Utah 1991), cites FDA regulation and the "unavoidably unsafe" nature of drugs as reasons not to impose strict liability. *Id.* at 90-92. This leaves to "courts to find liability under circumstances of inadequate warning, mismanufacture, improper marketing, or misinforming the FDA—avenues for which courts are better suited." *Id.* at 99.

[7] The gist of Professor Stapleton's argument is that the Europeans should learn from the U.S. experience and move away from a view that, at least rhetorically, treats liability for defective products, including drugs, as being strict. The leading European case on the character of liability is *A v. National Blood Authority*, [2001] 3 All ER 289 (Q.B.). It involves claims by Hemophiliacs given transfusions of blood infected by Hepatitis C. The court held the defendant liable, although the defendant was not negligent in failing to screen against Hepatitis C given the state of the art when the claims arose. The court interpreted the Product Liability Directive as intended to "achieve a higher and consistent level of consumer protection throughout the Community and render recovery of compensation easier, and uncomplicated by the need for proof of negligence." *Id.* at 310-11.

In particular, while it is now a minority position, some courts apply the "hindsight test" to determine whether a product was defective or, in the case of an FDA-approved drug, whether there was inadequate warning. The "hindsight test" assesses whether a product was defective—or, in the case of an FDA-approved drug, whether a warning was adequate—taking account of information that arose after a product was marketed. See *Sternhagen v. Dow Co.*, 935 P.2d 1139, 1147 (Mont. 1997); DAVID G. OWEN, PRODUCTS LIABILITY LAW § 8.7 (2005). A court that applies the hindsight test will hold a drug maker liable if risks that became apparent only in hindsight warranted an additional warning. The court would not be second-guessing the FDA's decision not to require such a warning for the agency does not have the benefit of hindsight.

Congress could decide that the interest in compensation is not sufficient to justify maintaining civil liability for failure to warn as a complement to FDA regulation. Congress has not done so here. To the contrary, recent legislation enacted in the wake of the Vioxx debacle expressly ratifies a regulatory requirement that a drug maker warn the public of risks the drug maker is aware of without waiting for action by the FDA.[8] It was well-known that this requirement is a linchpin of civil liability for it means FDA-approved warnings are not a ceiling on a drug maker's duty to warn.

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[8] See Food and Drug Administration Amendments Act of 2007, Pub. L. No. 110-85, § 901(a), 121 Stat. 823, 925-26 (codified at 21 U.S.C. § 355(*o*)(4)(I)) ("2007 FDA Amendments Act").

B. Regulating decisions outside the purview of the FDA's approval of a drug and its labeling.

Tort liability also has regulatory value. Sometimes it is a safeguard against regulatory failure. The FDA sometimes fails to protect the public from unreasonably dangerous drugs. The Vioxx experience is instructive:

> The picture that the Vioxx experience paints of FDA regulation of pharmaceutical products is one of an agency that has been very accommodating to the regulated industry in approving new and potentially highly beneficial drugs but not especially adept at detecting adverse side effects once these drugs are in use. At the same time, the pharmaceutical industry has been very aggressive in pushing potential "blockbuster" drugs through the approval process, and it has not been particularly forthcoming with the agency and the public when it comes upon warning signs of potential adverse outcomes. . . . Dr. David J. Graham . . . called the Vioxx episode "a profound regulatory failure," and he pessimistically concluded that "FDA as currently configured is incapable of protecting America against another Vioxx."

McGARITY, *supra*, at 16.

Regulatory failure has many causes. The FDA is inadequately funded and staffed, drug makers may withhold relevant information, the FDA may be subject to regulatory capture, and drug makers may resist FDA action. But even if the agency were ade-

quately funded and staffed, and drug makers always worked hand-in-hand with the agency to ensure the safety and efficacy of drugs, failure-to-warn liability would still be warranted to encourage drug makers to warn about risks that are outside the purview of the FDA's decision when it approves a new drug and its labeling. Indeed, state courts and legislatures generally agree that regulatory approval of conduct should shield an actor from liability only with regard to risks that the regulator considered in approving the conduct. These reasons for maintaining failure-to-warn liability are independent of the quality of the FDA's analysis in approving a drug and its labeling.

1. Post-marketing risk information.

Approval of a new drug usually is based on limited clinical studies involving relatively small populations and relatively short time periods. "Once the drug enters the marketplace, risks that are relatively rare, that manifest themselves only after an extended period of time, or that affect vulnerable subpopulations, begin to emerge. These are often not risks foreseen by the drug's manufacturer or the FDA and, for that reason, are not addressed on the label." David A. Kessler & David C. Vladeck, *A Critical Examination of the FDA's Efforts to Preempt Failure-to-Warn Claims*, 96 GEO. L.J. 461, 466 (2008) (footnote omitted). "[F]ully one-half the adverse effects of newly marketed drugs are not discovered until after the drugs have been on the market for a while." MCGARITY, *supra*, at 237-38.

Historically, the FDA has expended vastly more resources evaluating new-drug applications than it does monitoring adverse events with existing drugs. See Kessler & Vladeck, 96 GEO. L.J. at 485. Doctor

Kessler and Professor Vladeck describe new tools and resources given to the FDA by the 2007 FDA Amendments Act to strengthen the agency's post-approval surveillance. *Id.* at 487-90.[9] But they conclude "it remains to be seen whether this increased surveillance will help the agency to recognize emerging safety problems more quickly." *Id.* at 490. Some problems are endemic. It is difficult for the FDA to assess adverse reaction reports when it "does not know how many people are using the drug or have information about their conditions." *Id.* And it takes time for the FDA to take effective action, particularly if the information the FDA has is inconclusive and a drug company puts up resistance.[10]

2. "Off-label use."

Drugs often are prescribed for "off-label use," meaning a use that has not been approved by the FDA.[11] It is estimated that "40-60% of prescriptions

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[9] These include express statutory authority to update labeling and to order new clinical trials, something the FDA had done in the past depending on the cooperation of drug makers.

[10] An FDA advisory panel recommended in early 2001 that the Vioxx label warn about the cardiovascular risk. This recommendation was based on a study that showed a correlation but Merck argued there was another cause. "Merck vigorously resisted this suggestion, arguing that the gastrointestinal benefits of Vioxx outweighed any cardiovascular risk. After fourteen months of negotiations, Merck and the agency compromised" on a diluted warning. The FDA acted quickly to take Vioxx off the market once it received the results of a more conclusive study in September 2004. See MCGARITY, *supra*, at 7-8.

[11] Fisch, the physician assistant who gave the harmful injection to respondent, disregarded the specified dosage, giving respondent a 50-mg double dose. For this reason, and because the

were written for off-label uses" and that "50% of cancer treatment drugs, 80-90% of drugs used to treat rare diseases, and 80% of drugs used in the pediatric field are prescribed off-label to patients." James O'Reilly & Amy Dalal, *Off-Label or Out of Bounds? Prescriber and Marketer Liability for Unapproved Uses of FDA-Approved Drugs*, 12 ANNALS HEALTH L. 295, 298 (2003). The fighting issue regarding FDA regulation of off-label uses has been whether and to what extent drug makers may promote off-label uses or educate physicians and the public about off-label uses. The FDA can warn the public and physicians about an unreasonably risky off-label use, and the FDA can ask a drug maker to stop marketing a drug when it learns of unreasonably dangerous off-label use. But this is after the fact, sometimes tragically so.

Fen-Phen is a case in point. Fenfluramine was combined with Phentermine to create a dietary suppressant that did not make people fall asleep. The popular press reported the results of a study published in 1992 that found subjects who used Fen-Phen lost 30 pounds on average in 9 months. It was off to the races. By 1996, physicians had written over 5 million prescriptions for Fen-Phen. The FDA never approved the combination. By the time the FDA asked Wyeth in 1997 to stop marketing the drug and a sister drug, Redux, it is estimated that 45,000 women had been harmed by taking one or the other. See Sue McGrath, *Only a Matter of Time: Lessons Unlearned at the Food and Drug Administration Keep Americans at Risk*, 60 FOOD & DRUG L.J. 603,

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label did not approve administration of Phenergan by IV-push, this case involves an "off-label use" of a drug.

613-16 (2005); ALICA MUNDY, DISPENSING WITH THE TRUTH (St. Martin's 2001).

3. Unexamined risks.

Petitioner argues (at 3-4, 11-16, 33, 44) that the jury was asked to override the FDA's determination that the potential benefits of intravenous injection of Phenergan outweighed the risks. This misstates the theory on which the case was litigated and what the FDA actually approved. The case was litigated on the theory that Wyeth was negligent in failing to warn against administration of Phenergan by IV-push.

The labeling of Phenergan neither approved nor warned against administration of Phenergan by IV-push. The labeling recommended "deep intramuscular injection." It warned of the hazard of IV administration and included the following instruction:

> When used intravenously, Phenergan Injection should be given in a concentration no greater than 25 mg per mL and at a rate not to exceed 25 mg per minute. When administering any irritant drug intravenously, it is usually preferable to inject it through the tubing of an intravenous infusion set that is known to be functioning satisfactorily.

JA 390. The label permits IV administration but mentions administration only by IV-drip. It neither expressly approves nor warns against administration by IV-push. As best we know, the FDA Advisory Committee and other relevant decision-makers never addressed the question whether the risk of admin-

istration of Phenergan by IV-push outweighed the benefits.

II. Preemption of state-law tort claims based on FDA regulation of a drug is unnecessary because the civil justice system defers to FDA expertise and protects drug makers from spurious claims.

Petitioner's policy arguments for preemption paint a picture of a world in which courts and juries freely disregard the FDA's judgments about drug efficacy and safety and about labeling and a world in which drug makers have little protection from spurious claims. Unsurprisingly, the real world looks nothing like this. State courts and legislatures are well aware that drugs that do great good also often come with great risk. And they respect the expertise of the FDA in deciding whether the benefits of a new drug outweigh the risks and in deciding what risks merit warning. What they have steadfastly refused to do is to immunize drug makers from failure-to-warn liability in the absence of a decision by the FDA that the specific risk in question did not warrant warning. Only one state legislature, Michigan, has taken this step. Petitioner asks this Court to do something that neither Congress, nor any other state legislature, nor any state court has thought prudent.

A. Tort law already defers to FDA's expertise in drug approval.

Over the last half century, tort law has evolved to a position in which courts largely cede to the FDA the authority to decide whether a new drug should be allowed on the market. Drug makers face a risk

of liability only for failing to warn of a drug's risks. Professor Owen summarizes the story:

> Whether and how prescription drugs in particular should be treated differently from other types of products has consumed more time and effort, and resulted in the gnashing of more teeth, than about any other particular issue in all of products liability law. In addition to featuring two prominent Restatement provisions—comment k to § 402A of the Restatement (Second) of Torts and § 6(c) of the Third Restatement, the drug design defect story wends through two of the most prominent cases in products liability law history—*Feldman v. Lederle Laboratories* and *Brown v. Superior Court*. The issue is complex, involving the learned intermediary doctrine, product category liability, state of the art, the battle for supremacy between the consumer expectations and risk utility tests of liability for design defectiveness, the never-ending struggle between negligence and strict liability, how design and warning defect notions fit together, federal preemption, and, at bottom, whether drugs in fact are different from other types of products, and whether they should be treated differently by products liability law.

OWEN, *supra*, at 549.

Professor Owen refers to an ongoing debate over when and how FDA-approved drugs should be shielded from products-liability claims in general and design-defect claims in particular. The issue emerges only after true strict liability (sometimes

referred to as absolute liability) is rejected in favor of negligence-based liability. Once this choice has been made, drugs are the paradigmatic example of what has come to be called an "unavoidably dangerous" product. This is a product—like a cigarette, a gun, or a knife—that must be dangerous if it is to perform its intended function. Products liability law generally is open to a claim that an unavoidably dangerous product should be designed more safely so it could serve its intended function with reduced risk.

Debate exists whether the law should permit a claim that a product was so dangerous, and of so little utility, that it is wrong to sell the product even if it can be made no safer while performing its intended function. While this is hotly contested terrain, there is a consensus that FDA-approved drugs should be shielded from both types of claims. It is thought that the FDA, better than a judge or jury, can decide whether the benefits of a new drug sufficiently outweigh the risk to justify placing the drug on the market, and whether the design of a drug can be tweaked to realize the benefits with reduced risk.

The debate has been over precisely when and how an FDA-approved drug should be shielded from a design-defect claim. Some courts have adopted a categorical rule precluding design-defect claims for FDA-approved drugs. This is the approach taken in *Brown v. Superior Court*, 751 P.2d 470 (Cal. 1988), and adopted in cases such as *Grundberg v. Upjohn Co.*, *supra*.[12] Other courts have taken a case-by-case

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[12] The *Grundberg* court summarized the justification:

> We find this extensive regulatory scheme capable of and appropriate for making the preliminary deter-

approach. Under this approach, the judge makes a preliminary determination whether a drug was defective as marketed or as designed. This is the approach taken in *Feldman v. Lederle Laboratories*, 479 A.2d 374 (N.J. 1984), and adopted and amplified in cases such as *Freeman v. Hoffman-La Roche, Inc.*, 618 N.W.2d 827 (Neb. 2000). This takes the issue out of the hands of the jury. The Restatement (Third) of Torts: Products Liability § 6(c) (1998) straddles the two approaches by supplying a rule that allows a claimant to proceed with a design-defect claim only if the foreseeable risks are so great, and foreseeable benefits so small, that no health-care professional would prescribe the drug "for any class of patients." Professor Owen observes that this "leaves a very small window for design defect claims for prescription drugs, a window so tiny that almost no drug claim could fit through it." OWEN, *supra*, at 557.

The upshot is that courts generally have ceded to the FDA the power to determine whether a new drug should be placed on the market as designed, so long as the drug maker is not aware of risks that it fails to disclose to the FDA. While ceding this ground, courts have retained failure-to-warn liability. Thus,

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mination regarding whether a prescription drug's benefits outweigh its risks. The structured follow-up program imposed by law ensures that drugs are not placed on the market without continued monitoring for adverse consequences that would render the FDA's initial risk/benefit analysis invalid. Allowing individual courts and/or juries to continually reevaluate a drug's risks and benefits ignores the processes of this expert regulatory body and the other avenues of recovery available to plaintiffs.

813 P.2d at 97.

the Utah Supreme Court observed in *Grundberg*, 813 P.2d at 99: "Relying on the FDA's screening and surveillance standards enables courts to find liability under circumstances of inadequate warning, mismanufacture, improper marketing, or misinforming the FDA—avenues for which courts are better suited." This compromise facilitates getting new drugs on the market while using failure-to-warn liability to encourage dissemination of information about risks and so enable health-care professionals and the public to make informed decisions about drugs.

B. *Daubert* and the "learned intermediary doctrine."

Other judicially developed doctrines address specific policy arguments for preemption. One argument raises the specter of unsophisticated juries overriding the FDA based on junk science. Fifteen years ago, this Court, in *Daubert v. Merrell Dow Pharmaceuticals, Inc.*, 509 U.S. 579 (1993), interpreted Rule 702 of the Federal Rules of Evidence to empower trial judges to screen proffered expert scientific testimony to ensure that the testimony meets basic standards of scientific validity and reliability. Professor Owen observes: "Post-Daubert, the federal district courts, exercising their newly appointed 'gatekeeper' function, have scrutinized expert testimony more closely, often holding rigorous pre-trial 'Daubert hearings'—that are often outcome determinative—to determine the admissibility of proffered expert testimony." David G. Owen, *A Decade of Daubert*, 80 DENV. U. L. REV. 345, 362 (2002). While counts vary, it is estimated that a majority of states

now apply a similar standard. See OWEN, *supra*, at 376.

Another argument raises the specter of drug makers responding to the risk of liability by overwhelming consumers with warnings. This is avoided by the "learned intermediary" doctrine, which shields makers of prescription drugs from claims for failure to warn the public.[13] One codification of the doctrine states:

> [A prescription] drug is not defective due to inadequate warning or instruction if its manufacturer provides otherwise adequate warning and instruction to the physician or other legally authorized person who prescribes or dispenses that [prescription] drug for a claimant in question and if the federal food and drug administration has not provided that warning or instruction relative to that [prescription] drug is to be given directly to the ultimate user of it.

Ohio Rev. Code Ann. § 2307.76(C).

The learned intermediary doctrine obviates the need for preemption in one of the situations described by the FDA in the preamble to the 2006 labeling regulations.[14]

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[13] "The doctrine was first recognized in case law over 50 years ago, and since that time has been recognized and applied in nearly all jurisdictions in the country." Richard B. Goetz & Karen R. Growdon, *A Defense of the Learned Intermediary Doctrine*, 63 FOOD & DRUG L.J. 421, 421 (2008).

[14] The preamble states preemption is justified of "[c]laims that a drug sponsor breached an obligation to warn by failing to

C. The defense of regulatory compliance.

The ALI, state courts, and state legislatures have been grappling with the general question of whether and when civil courts and juries should defer to regulatory approval of allegedly negligent conduct in considering what has come to be called the defense of regulatory compliance. A broad consensus holds that regulatory approval of conduct should shield an actor from negligence liability only if the regulator considered the specific risk in question when it approved the conduct.

1. The evolving views of the ALI.

Over the last generation, the ALI has slowly moved towards a position that treats regulatory approval of allegedly negligent conduct as a basis for taking the issue of negligence away from the jury if the regulator considered the specific risk in question and decided that additional precautions were not worth taking.

While stating the traditional common-law position that statutes and regulations set a floor and not a ceiling on what is reasonable conduct, Restatement (Second) of Torts § 288C (1965) briefly acknowledges in Comment *a* the possibility that a court may treat a statute or regulation as determinative of what is reasonable conduct:

> [A] legislative or administrative minimum does not prevent a finding that a reasonable

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include in an advertisement any information the substance of which appears anywhere in the labeling, in those cases where a drug's sponsor has used Highlights consistently with FDA draft guidance regarding the 'brief summary' in direct-to-consumer advertising." 71 FED. REG. at 3936.

> man would have taken additional precautions where the situation is such as to call for them. . . . Where there are no such special circumstances, the minimum standard prescribed by the legislation or regulation may be accepted by the triers of fact, or by the court as a matter of law, as sufficient for the occasion . . . .

More recent Restatements expand on when a court may take the issue of the unreasonableness of conduct or the defectiveness of a product away from the jury because of legislative or regulatory approval of the conduct or product. Restatement (Third) of Torts: Products Liability § 4 (1998) explains in Comment *e*:

> Occasionally, after reviewing relevant circumstances, a court may properly conclude that a particular product safety standard set by statute or regulation adequately serves the objectives of tort law and therefore that the product that complies with the standard is not defective as a matter of law. Such a conclusion may be appropriate when the safety statute or regulation was promulgated recently, thus supplying currency to the standard therein established; when the specific standard addresses the very issue of product design or warning presented in the case before the court; and when the court is confident that the deliberative process by which the safety standard was established was full, fair, and thorough and reflected substantial expertise. Conversely, when the deliberative process that led to the safety

> standard with which the defendant's product complies was tainted by the supplying of false information to, or the withholding of necessary and valid information from, the agency that promulgated the standard or certified or approved the product, compliance with regulation is entitled to little or no weight.

Restatement (Third) of Torts: Liability for Physical Harm § 16 (Proposed Final Draft No. 1, 2005), after canvassing the situations in which compliance is not a defense, explains in Comment *f* when compliance may be a defense:

> *Statutory compliance as a limitation on liability.* While the Comments above explain the rule to the effect that compliance with statutes is usually no more than evidence of nonnegligence, the observations in the Comments suggest the rule's own limits. When the statute directly addresses the particular safety problem before the court, when the statutory scheme evidently seeks to identify all the precautions called for by the general negligence standards in § 3, and when the particular case involves no unusual circumstances, the court may conclude that the actor's compliance with the statute shows that the actor's conduct does not lack reasonable care. In reaching this conclusion, the court can take into account several factors, including the evident thoroughness of the statute and the desirability of a uniform liability standard that can simplify litigation and

> provide parties with appropriate guidance as to what precautions are expected of them.

ALI's Reporters' Study, *Enterprise Responsibility for Personal Injury* (1991), goes furthest towards endorsing a strong defense of regulatory compliance. After stating that, at a minimum, regulatory compliance should create a presumption of non-negligence and should shield an actor from punitive damages, the study goes on to recommend "making regulatory compliance a complete bar to tort liability once certain carefully-defined conditions have been satisfied respecting the regulation." *Id.* at 110. One condition is that "[t]he agency must have addressed the specific risk at issue in the case at hand, and must have made an explicit judgment about what type of legal controls are appropriate." *Id.* This condition is not satisfied in this case because the FDA never addressed the specific risk of administration of Phenergan by IV-push.

2. The defense of regulatory compliance in the courts.

Courts that have endorsed a defense of regulatory compliance limit the defense to cases in which the regulator considered the specific risk at issue in approving the challenged conduct. Justice Linde expressed the requirement pithily in a concurring opinion in *Wilson v. Piper Aircraft*, 577 P.2d at 1334-35:

> [I]t should be defendant's burden to show that a governmental agency has undertaken the responsibility of making substantially the same judgment that the court would otherwise be called on to make; and if so, it should

> then be plaintiff's burden to show that the responsible agency has not in fact made that judgment with respect to the particular "defect" at issue.

One leading case, *Ramirez v. Plough, Inc.*, 863 P.2d 167 (Cal.1993), involved a challenge to the labeling of a non-prescription drug. The plaintiff claimed it was negligent to market children's aspirin in California without a warning in Spanish of the risk of Reye's Syndrome. The California Supreme Court, affirming summary judgment for the defendant, found the FDA's decision not to require a Spanish-language warning conclusive on the issue of negligence: "[T]he FDA has concluded that despite the obvious advantages of multilingual package warnings, the associated problems and costs are such that at present warnings should be mandated only in English." *Id.* at 175.[15] In other words, court ruled for the defendant only because it concluded that the FDA had considered the relevant cost and benefits and decided the cost outweighed the benefits.

3. State legislation.

State legislatures have moved cautiously in making regulatory approval of conduct or a product a defense to a claim that the conduct was unreasonable or the product was defective. Regulatory approval of conduct or a product is generally relevant under

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[15] The bases for this conclusion were that the FDA required Spanish-language warnings on medicine sold in Puerto Rico and other territories where the predominant language was Spanish, 863 P.2d at 174, and the FDA had experimented with foreign-language package inserts but concluded that the cost outweighed the benefits, *id.* at 175.

state statutes only if the regulator specifically addressed the risk at issue in a case, and the approval creates only a presumption of non-negligence and non-defectiveness. Only Michigan has enacted a statute that shields a drug maker from liability for failure to warn about risks that the FDA did not consider in approving a drug and its labeling. Some states have enacted statutes that make FDA approval of a drug and labeling a general shield to liability for punitive damages, even with regards to risks not considered by the FDA.

a) Presumption of non-negligence and non-defectiveness.

A significant number of states have enacted statutes that provide for a rebuttable presumption of non-negligence and non-defectiveness if a regulator approves of conduct or a product. Some of the statutes are general while some apply only to FDA-approved drugs and labeling. See Ark. Code Ann. § 16-116-105; Colo. Rev. Stat. § 13-21-403; Fla. Stat. § 768.1256(1); Ind. Code § 34-20-5-1; Kan. Stat. Ann. § 60-3304(a) (enacting Model Uniform Product Liability Act § 108(A)[16] verbatim); Mich. Comp. Laws § 600.2946(4); N.J. Stat. Ann. § 2A:58C-4 (warning or instruction in compliance with regulatory approval under the Federal Food, Drug, and Cosmetic Act and the Public Health Service Act); N.D. Cent. Code

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[16] The Model Uniform Product Liability Act was published by the Department of Commerce in 1979. See 44 FED. REG. 62,714 (Oct. 31, 1979).

§ 28-01.3-09; Tenn. Code Ann. § 29-28-104; Tex. Civ. Prac. & Rem. Code Ann. § 82.007.[17]

The rebuttable presumption is not toothless. *Schultz v. Ford Motor Co.*, 857 N.E.2d 977 (Ind. 2006), holds that the jury is told of the presumption. This invites the jury to defer to an agency if they are uncertain about whether a product was unreasonably dangerous. One court has gone further and endorsed instructing the jury that regulatory compliance is "strong and substantial evidence" of non-negligence and non-defectiveness. *Lorenz v. Celotex Corp.*, 896 F.2d 148, 149 (5th Cir. 1990) (Texas law).

The Vermont legislature has not enacted such legislation. Even if it had, the presumption would not have applied in this case because the FDA did not approve administration of Phenergan by IV-push. The presumption applies only if "the specific injury causing aspect of the product conformed to or was in compliance with the legislative or administrative regulatory standard." *Alvarado v. J.C. Penney Co.*, 735 F. Supp. 371, 373 (D. Kan. 1990) (quoting the comments to § 108 of the Model Uniform Product Liability Act). See also *Ehlis v. Shire Richwood, Inc.*, 233 F. Supp. 2d 1189, 1198-99 (D.N.D. 2002) (holding the presumption does not apply to an "off-label" use because the use was not approved by the FDA), *aff'd*, 367 F.3d 1013 (8th Cir. 2004).

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[17] Washington Revised Code § 7.72.050(1) merely provides that the trier of fact may consider evidence of compliance. This was to reverse a Washington case holding that the evidence was not admissible.

b) A shield against punitive damages.

Several states have statutes that shield drug manufacturers from punitive damages if a drug is manufactured and labeled in accordance with FDA approval. See Ariz. Rev. Stat. § 12-701; N.J. Stat. Ann. § 2A:58C-5(c); N.D. Cent. Code § 19-02.1-26(1); Ohio Rev. Code Ann. § 2307.80(C); Or. Rev. Stat. § 30.927; Utah Code Ann. § 78B-8-203. Typically, the shield is removed if a manufacturer knowingly withholds relevant information from the FDA.[18] Unlike the presumption, these statutes do not require that the FDA have considered the specific risk at issue. See, e.g., Ariz. Rev. Stat. § 12-701.

c) The Michigan statute.

In 1995, Michigan enacted a statute providing "a drug is not defective or unreasonably dangerous, and the manufacturer or seller is not liable, if the drug was approved for safety and efficacy by the United States food and drug administration, and the drug and its labeling were in compliance with the United States food and drug administration's approval at the time the drug left the control of the manufacturer or seller." Mich. Comp. Laws § 600.2946(5). The statute was upheld in *Taylor v. SmithKline Beecham Corp.*, 658 N.W.2d 127 (Mich. 2003).

The statute is unique in its breadth. It shields a drug maker from any liability based on a theory of negligence or products liability if a drug has been approved by the FDA. Unlike the defense of regula-

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[18] *McDarby v. Merck & Co.*, 949 A.2d 223, 271-76 (N.J. Super. Ct. App. Div. 2008), holds that this feature of the New Jersey statute is preempted under the logic of *Buckman Co. v. Plaintiffs' Legal Committee*, 531 U.S. 341 (2001).

tory compliance and the statutes creating a rebuttable presumption, the defense is not limited to claims involving risks actually addressed by the FDA. There is no exception for risks that appear post-marketing. And there is no exception for "off-label" uses the FDA never approved. The only exceptions are (i) if a company intentionally withholds information that it is required to submit under federal law that would have led the FDA not to approve the drug, or to withdraw approval, and (ii) if an FDA official is bribed.

III. This Court should leave it to Congress to craft appropriate preemption rules.

Preemption is not a simple either-or proposition. A narrow rule of preemption is similar to a strong form of the defense of regulatory compliance. It would make FDA approval of drug labeling determinative of non-negligence and non-defectiveness if the FDA considered the specific risk at issue in a case and concluded the labeling provided sufficient warning with respect to that risk. A state could still impose strict liability that did not require a finding that it was negligent to fail to give additional warning. In addition, liability would not be precluded if the FDA did not consider the specific risk at issue in approving the drug and labeling. Thus, a drug maker would be subject to liability if it had reason to know the labeling was deficient based on post-marketing risk information if the FDA had not yet considered whether the information justified additional warning. A drug maker would be liable for failure to warn about "off-label" uses not approved by the FDA. And a drug maker would be liable if the FDA did not consider the specific risk at issue (as in this case,

because the FDA did not approve administration of Phenergan by IV-push). Additional exceptions might also be made for cases in which a drug maker withholds relevant risk information to the FDA or unduly influences the FDA's decision.

A broad form of preemption would be similar to the Michigan statute. It would shield a drug maker from all claims regarding an FDA-approved drug and labeling so long as the drug maker complied with the FDA's orders. A claim would be precluded even if the FDA did not consider, and could not have considered, the relevant risk when approving labeling. While the Michigan statute makes exception for cases in which a drug maker withholds crucial risk information, or in which a drug maker bribes an FDA official, one could dispense even with these exceptions.

There are intermediate possibilities. A narrow form of preemption could be supplemented by a rule precluding a state from imposing strict liability. And drug makers could be shielded from punitive damages.

Ideally, Congress or, in the absence of congressional action, state legislatures should choose among alternative preemption rules because the choice turns on fundamental questions of morality and policy on which there is deep disagreement, as well as contestable empirical assumptions. The choice only obliquely turns on views of the relative strengths and weaknesses of the FDA and courts in regulating drug warnings.

In particular, Congress can best weigh the interests in corrective justice and compensation, which

justify civil liability, against the concerns for litigation cost and error, and the interest in national uniformity, which justify preemption. The political branches are also in the best position to give due weight to the fundamental federalism concerns that would be raised by any effort to preempt such basic and well-established state-law tort principles. Finally, institutional concerns point to Congress. Congress can legislate rules that resolve predictable boundary-drawing problems. This Court can resolve only the particular case before it. It would require a series of cases to define even the most general contours of preemption.

A possible alternative might be to have the FDA rule on a case-by-case basis, as it approves a particular drug and labeling, whether, and the extent to which, preemption of civil liability is warranted. The agency has done this in the past by rulemaking in specific situations when it deemed it warranted.[19]

Congress should also decide whether a preemption rule applies retroactively or prospectively. Until the FDA's recent change of position, it was generally assumed that FDA approval of a drug and labeling did not shield a drug maker from failure-to-warn liability, particularly for risks that the FDA did not consider in approving the labeling. FDA officials may well have rested easier in approving a drug and its labeling because they knew they were not solely responsible for protecting the public from unreasonably dangerous drugs. Certainly they would not have thought the legal system expected them to be

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[19] Examples are collected at 71 FED. REG. at 3935.

omniscient and to anticipate post-marketing risks and off-label uses.

CONCLUSION

The judgment of the Supreme Court of Vermont should be affirmed.

Respectfully submitted,

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APPENDIX

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In The

Supreme Court of the United States

WYETH,
Petitioner,
v.
DIANA LEVINE,
Respondent.

On Writ Of Certiorari To
The Vermont Supreme Court

BRIEF OF *AMICI CURIAE* DAVID B. ROSS, M.D., Ph.D. AND STEFAN P. KRUSZEWSKI, M.D. IN SUPPORT OF RESPONDENT

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INTEREST OF *AMICI CURIAE*[1]

Amici curiae are physicians who have performed extensive work in the public and private sectors researching, evaluating, and bringing to public light information pertaining to the safety and efficacy of prescription drugs. *Amici* have a strong interest in the federal preemption issue before the Court in this case based on their and their colleagues' direct involvement with government regulation and private marketing of prescription drugs. *Amici* believe that the resolution of this case could have a significant impact on the health and safety of patients and the public at large who depend on state tort law and other public processes to help ensure the safety and efficacy of prescription drugs that are approved for specific uses by the Food and Drug Administration ("FDA"). *Amici* thus submit this brief in support of Respondent urging the Court to hold that the FDA's approval of a prescription drug's label does not preempt state tort law claims for failure to warn consumers of health and safety risks caused by the drug.

Dr. David B. Ross received his M.D. and Ph.D. (Biochemistry) from the New York University School of Medicine. After completing a categorical internal

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[1] Letters granting blanket consent to the filing of *amicus curiae* briefs have been filed with the Clerk. This brief was not authored in whole or in part by counsel for a party. No person or entity other than *amici curiae* or their counsel made a monetary contribution to the preparation or submission of this brief.

medicine residency at NYU, Dr. Ross received fellowship training in infectious diseases at Yale University School of Medicine, and subsequently was a member of the faculty there. From 1996 until 2006, Dr. Ross served as a medical officer at the FDA, first as a medical reviewer and team leader in FDA's division of Anti-Infective Drug products, then as deputy director of the FDA office reviewing therapeutic biologic products (Office of Drug Evaluation VI), and subsequently as associate director of FDA's Office of Oncology Drug Products. During his time at FDA, Dr. Ross was involved in the review of a number of high-profile drug applications, including the first new class of antibiotics to be approved in three decades, the first monoclonal antibody used to treat multiple sclerosis, and the first oral drug for treatment of iron overload. He also worked extensively on medical countermeasures against biological weapons. Since 2006, Dr. Ross has been Director of Clinical Public Health Programs at the Department of Veterans Affairs, where he oversees the Department's National HIV and Hepatitis C Programs. Dr. Ross also holds an appointment as Associate Clinical Professor of Medicine at George Washington School of Medicine and Health Sciences. Dr. Ross's article, *The FDA and the Case of Ketek*, 356 N. ENG. J. MED. 1601 (Apr. 19, 2007), is cited and discussed extensively herein.

Dr. Stefan P. Kruszewski received his M.D. from Harvard Medical School in 1977. He then completed a Medical Internship at New England Deaconess Hospital, a Psychiatric Residency and Fellowship

at the University of Medicine and Dentistry of New Jersey/Robert Wood Johnson Medical School, and a Mini Fellowship at Duke University. He subsequently served as Chairman of the Department of Psychiatry at Conemaugh Memorial Hospital in Johnstown, Pennsylvania and as Director of the Geriatric Neuropsychiatric Institute and Associate Director of Psychiatric Residency at the Allegheny Neuropsychiatric Institute, an affiliate of Allegheny General Hospital in Pittsburgh. Starting in 2001, Dr. Kruszewski served as Psychiatric Consultant for the Pennsylvania Department of Public Welfare, where he performed medical reviews of the services provided by treatment facilities, including their use of prescription medications. He was terminated from this position after reporting systemic abuses at these facilities, including widespread and improper prescriptions of antipsychotic medications for off-label uses. Dr. Kruszewski also has served on the faculty of Eastern University and the Penn State College of Medicine. Dr. Kruszewski was recognized as a "distinguished" expert whose testimony was deemed admissible in the mass tort case *In re Zyprexa Products Liability Litig.*, 489 F. Supp. 2d 230, 267 (E.D.N.Y. 2007), involving a prescription antipsychotic drug whose safety and off-label uses are discussed herein.

Amici submit this brief to inform the Court about the deficiencies and abuses that they and their colleagues have witnessed and brought to light through their involvement with the FDA's prescription drug approval process and the subsequent marketing of

these drugs. *Amici* believe that the deficiencies and abuses discussed herein help demonstrate that adoption of Petitioner's and its *amici*'s sweeping federal preemption arguments would undermine the public health and safety goals of the Food, Drug, and Cosmetic Act ("FDCA"), 21 U.S.C. §§ 301 *et seq.*

INTRODUCTION AND SUMMARY OF ARGUMENT

Petitioner's argument (Brief at 40) that the FDA functions as an "expert scientific agency [that] makes uniform, national judgments about the safety and effectiveness of prescription drugs by balancing therapeutic benefits against safety risks," and, in so doing, acts as the "ultimate regulator of the labeled conditions of use for which a drug is approved," is not borne out as a matter of law or fact. Respondent (Brief at 25-31) demonstrates the lack of statutory support for this argument, and *amici* will not repeat her analysis, save to emphasize that there has been no showing of a "'clear and manifest'" intent by Congress to make FDA the exclusive regulator of prescription drug safety by preempting a field that, at least to the extent of compensating injury victims, has been "'traditionally occupied by the States.'" *English v. General Electric Co.*, 496 U.S. 72, 79 (1990), quoting *Jones v. Rath Packing Co.*, 430 U.S. 519, 525 (1977) (internal citation omitted). Indeed, Congress's intent *not* to enact a sweeping preemption regime for prescription drug safety is proven by the

fact that Congress expressly stated its intent elsewhere in the FDCA to preempt state laws pertaining to medical devices, 21 U.S.C. § 360k(a), while expressing no such intent with regard to drug labeling. *See Riegel v. Medtronic, Inc.*, 128 S. Ct. 999, 1009 (2008); *cf. Bates v. Dow Agrosciences, LLC*, 544 U.S. 431, 449 (2005) (addressing statute's express preemption language as basis for rejecting product manufacturer's field preemption argument).

Instead, this brief focuses on specific examples that show the FDA's failure or inability to carry out its statutory duty of ensuring prescription drug safety and efficacy in order to highlight the adverse public health and safety consequences that would result from these preemption arguments. The FDA is charged by statute with "ensuring that . . . human and veterinary drugs are safe and effective." 21 U.S.C. § 393(b)(2)(B). But the FDA has repeatedly failed to carry out these mandates at both the drug-approval and the post-approval marketing stages of its regulatory process.

At the approval stage, the FDA routinely fails to require sufficient and reliable evidence that is necessary to ensure that prescription drugs are safe and effective before they are marketed. *See, generally*, Carpenter, *et al.*, *Drug-Review Deadlines and Safety Problems*, 358 N. ENG. J. MED. 1354, 1359 (Mar. 27, 2008). For example, the FDA approved the antibiotic Ketek for marketing in 2004 despite the fact that the safety tests ordered by its advisory committee had resulted in submissions of fabricated safety data – a

fact that FDA officials *deliberately withheld from the advisory committee that was reviewing Ketek and recommended its approval*. *See* Ross, *supra*, at 1602. Within three years of its approval, Ketek was linked to dozens of cases of acute liver failure, at least four of which resulted in death, while serious questions persisted about the drug's efficacy. *See id.* at 1602-03.

At the post-approval marketing stage, the FDA is widely recognized as lacking the resources and capacity for effective regulation of drugs whose hazards become apparent after there is widespread use in the market. An example of the FDA's failure in this regard is the agency's inability to prevent unlawful promotion of unapproved uses of prescription drugs. *See* U.S. Gov't Accountability Office, *Prescription Drugs: FDA's Oversight of the Promotion of Drugs for Off-Label Uses*, GAO-08-835, at 5-16 (July 2008) (finding that FDA lacks any formal process for tracking drug promotion submissions, has extremely limited staffing, and lacks any separate oversight activity for off-label uses). The FDA's inability to enforce the statutory prohibition against promotions for off-label uses, *see* 21 U.S.C. § 331(a) and (d), is illustrated in the case of the antipsychotic drug Zyprexa. The FDA approved Zyprexa in 1996 for treatment of adult schizophrenia and bipolar disorder. But its manufacturer was shown, largely through documents obtained in private tort and state Medicaid litigation, to have encouraged promotion of off-label uses such as treatment of pediatric conditions, dementia, and dementia-related psychosis for which

its effectiveness was never demonstrated to the FDA. *See* Berenson, *Drug Files Show Maker Promoted Unapproved Use*, N.Y. Times, Dec. 18, 2006; Berenson, *Lilly E-Mail Discussed Off-Label Drug Use*, N.Y. Times, Mar. 14, 2008. At the same time, as Zyprexa was being prescribed to tens of millions of patients worldwide, there was substantial evidence linking antipsychotic drugs to the onset of diabetes and excessive weight gain, neither of which was mentioned on Zyprexa's originally approved warning label. *See In re Zyprexa Products Liability Litig.*, *supra*, at 249-53.

In light of these and other well documented failures by the FDA to ensure the safety and efficacy of approved prescription drugs, the Court should reject Petitioner's and its *amici*'s sweeping preemption arguments that would make the FDA the nation's sole regulator of drug safety. Such a result would be contrary – and indeed detrimental – to the health and safety goals of the FDCA itself.

ARGUMENT

I. THE FDA'S APPROVAL OF KETEK AND AVANDIA DEMONSTRATES A FAILURE TO ENSURE PRESCRIPTION DRUG SAFETY AND EFFICACY.

Petitioner's and its *amici*'s arguments for vesting exclusive authority in the FDA to regulate prescription drug labeling and safety are predicated upon

unfounded assumptions about the agency's ability and willingness to demand sufficient proof of safety and efficacy before it approves drugs for marketing. In fact, the past decade alone has witnessed a number of instances where high-profile prescription drugs approved by the FDA were shown to pose life-threatening health risks to patients. *See* Curfman, *et al.*, *Why Doctors Should Worry About Preemption*, 359 N. ENG. J. MED. 1, 2 (July 3, 2008). Whether or not these cases by themselves demonstrate failures by the FDA, a closer look at two recently approved drugs raises serious questions about the agency's ability and willingness to ensure the safety and efficacy of prescription drugs before they are marketed.

First, the process through which the FDA granted approval of the antibiotic Ketek demonstrates a serious failure to demand sufficient and reliable evidence of either the product's safety or its efficacy. Ketek was presented as the first of a new class of antimicrobial agents that circumvent antibiotic resistance. Ross, *supra*, at 1601. In its initial review, the FDA's advisory committee asked Ketek's manufacturer to conduct a study to obtain additional safety data for patients likely to use the drug, in part based on concerns about an apparent association with liver damage. *Id.* The ensuing study of Ketek, known as "study 3014," compared the incidence of hepatic, cardiac, and visual adverse events in patients taking Ketek with those in patients taking an approved therapy. *Id.* This study was conducted over five months, with more than 24,000

subjects, and purported to show that Katek was as safe as the comparison treatment. *Id.*

In fact, FDA inspections of the largest testing sites identified serious concerns of fraud, resulting in referrals of four of the largest sites for criminal investigation. *Id.* at 1602.[7] The physician who enrolled the most patients, more than 400, was found to have completely fabricated patient data and was sentenced to 57 months in prison for her fraudulent conduct in this testing. *Id.* at 1601-02; *see also* Letter from Senator Charles E. Grassley, Chair U.S. Senate Committee on Finance, to FDA Commissioner Andrew C. Von Eschenbach, Dec. 13, 2006 ("Grassley Letter") at 4-9. The FDA's Office of Criminal Investigation ("OCI") initially recommended to the drug Review Division and the Division of Scientific Investigation ("DSI") that "careful consideration" be given to use of data from this physician's testing site. Grassley Letter at 8. A DSI official raised further concerns about the second and third largest testing sites, including investigatory findings of over-enrollment, inadequate safety-related documentation, untimely record keeping, and improper shipping of laboratory samples. *Id.* at 10. Other "red flags" raised

[7] The discovery of these site deficiencies appears to be fortuitous in light of recent findings that the FDA inspects fewer than one percent of new drug and device testing sites. *See* Department of Health and Human Services Office of Inspector General, *The Food and Drug Administration's Oversight of Clinical Trials*, OEI-01-06-00160 at 19 (Sept. 2007).

by study 3014 included the manufacturer's decision to exclude testing data from two other sites and a widespread failure to adhere to the study's patient enrollment protocol for test sites. *Id.* at 11.

Faced with these irregularities and concerns about fraudulent data, the FDA's Review Division could have refused to submit the study 3014 data to the Ketek advisory committee, as the official charged with presenting the data recommended *Id.* at 14. Alternatively, it could have submitted the data along with the evidence of fraud uncovered by the ongoing criminal investigations. But instead, the Review Division chose a third option. It presented study 3014 to the advisory committee in January 2003 *without disclosing or making any mention whatsoever of the data irregularities and ongoing criminal fraud investigation.* *Id.* at 2-3, 5-6. Unaware of these problems with the reliability of the safety data before it, the advisory committee voted 11 to 1 to recommend approval of Ketek. *Id.* at 5-6.

In deciding to submit the study 3014 results without disclosing the ongoing fraud investigation, the Review Division's Office Director stated that "*I don't believe spending time on these issues in front of the [advisory committee] will be productive.*" *Id.* at 7 (emphasis added). The DSI's Division Director later contended that releasing information from an ongoing criminal investigation "would not only have been unprecedented and a violation of due process, but also would not have provided any meaningful context for committee consideration." *Id.* at 17. Four years after

this occurred, FDA officials stood by the decision to conceal evidence and concerns about fraudulent safety data from the advisory committee, explaining in response to Dr. Ross's article that *"[t]he FDA did not discuss data-integrity issues at the second advisory committee meeting to avoid compromising the ongoing investigations . . . "* Soreth, *et al.*, *Ketek – The FDA Perspective*, 356 N. ENG. J. MED. 1675 (April 19, 2007). But this does not explain why, given concerns over the reliability of the testing data and allegations about the process by which it was gathered, FDA officials decided to present study 3014 to the advisory committee *at all* while these investigations were still in progress. Ross, *supra*, at 1602.

Subsequent FDA reviews of Ketek's safety and efficacy were likewise based on problematic data. For example, the agency relied on foreign post-marketing reports on Ketek as evidence of its safety, without verifying their accuracy or completeness, even though these reports typically do not serve as a primary basis for determining safety. *Id.* Similarly, in assessing Ketek's efficacy, the agency relied on "noninferiority trials" that are meant not to demonstrate a product's superiority to existing treatments, but rather to show the "maximum margin by which the new invention may be less effective than older inventions but still be considered better than placebos." *Id.* By 2004, when Ketek was nearing final approval, the use of noninferiority trials to demonstrate a drug's efficacy was considered unsound. *Id.*; *see also* Powers, *Noninferiority and Equivalence Trials: Deciphering 'Similarity'*

of Medical Interventions, 27 STATISTICS IN MEDICINE 343 (Feb. 10, 2008) ("Inappropriate [noninferiority] trials have great clinical relevance since they may lead to approval by regulatory agencies of medical interventions whose benefits compared with placebo are unclear, and can start investigators down a slippery slope of comparing one potentially ineffective intervention to another in perpetuity."). The agency's rationale for accepting use of noninferiority trials in the case of Ketek was the need to stand by earlier agreements with the drug's sponsor. Ross, *supra*, 1602-03; Soreth, *supra*, 1675.

The FDA's approval of Ketek in 2004 thus was based in significant part on fraudulent safety data and other unreliable evidence as to the product's efficacy. In light of this checkered FDA approval history, the results of Ketek's use on patients are not surprising. Within seven months of the drug's launch, the first death of a Ketek user from liver failure was reported in a patient being treated for a mild respiratory tract infection. *See* Ross, *supra*, at 1603. Less than a year later, a single medical center reported a cluster of three cases of Ketek-associated liver failure, one fatal. *Id.* Nonetheless, the FDA continued to trumpet Ketek's safety, *citing study 3014 as evidence for this assertion*. *Id.* By the end of 2006, Ketek was associated with 53 cases of hepatotoxic effects, including 23 cases of acute severe liver injury, and 12 cases of acute liver failure, four of which were fatal. *Id.*

The FDA's approval of Ketek for marketing in the absence of reliable safety or efficacy data is not

unique. In 1999, the FDA approved the "wonderdrug" Avandia (rosiglitazone) for treatment of hyperglycemia for type 2 diabetes. Psaty and Furberg, *Rosiglitazone and Cardiovascular Risk*, 356 N. ENG. J. MED. 2522 (June 14, 2007). At the time of its approval, Avandia had been shown through small, short-term (up to 26 week) trials to reduce levels of fasting glucose and glycated hemoglobin by about one percent. *See id.* at 2522-23. But this result was not measured against the drug's longer term health effect in causing increase in body weight, fluid retention, and anemia. *See id.* Instead, the FDA approved the drug without the benefit of any long-term studies on its overall health effects on diabetics, and the drug was soon being prescribed to millions of patients. *See id.* at 2523.

In June 2007, eight years after FDA approval, a meta-analysis of treatment trials concluded that Avandia was associated with a significant (43%) increase in risk of heart attack and a slight increase in risk of death from cardiovascular causes. Nissen and Wolski, *Effect of Rosiglitazone on the Risk of Myocardial Infarction and Death From Cardiovascular Causes*, 356 N. ENG. J. MED. 2451, 2457 (June 14, 2007). This meta-analysis of Avandia echoed the view that the trial studies "were not adequately powered to determine the effects of this agent on microvascular or macrovascular complications of diabetes, including cardiovascular morbidity and mortality." *Id.* at 2458. The authors recognized that even their own data were incomplete and that there still was an "urgent

need for comprehensive evaluations to clarify the cardiovascular risks of [Avandia]." *Id.* at 2469. Despite these limitations, the authors concluded that Avandia was associated with a significant increase in the risk of heart attack and a borderline increase in risk of death from cardiovascular causes. *Id.* at 2467.

Analysts looking at this study of an undertested but nevertheless approved drug used by tens of millions of patients concluded that Avandia "represents a major failure of the drug-use and drug-approval processes in the United States." Psaty and Furberg, *supra*, 2523. The chair of the FDA's post-approval advisory committee for Avandia concurred:

> The basic plot of the rosiglitazone story quickly became obvious to the advisory committee: a new 'wonder drug,' approved prematurely and for the wrong reasons by a weakened and underfunded government agency subjected to pressure from industry, had caused undue harm to patients.

Rosen, *The Rosiglitazone Story – Lessons From an FDA Advisory Committee*, 357 N. ENG. J. MED. 844 (Aug. 30, 2007).

Despite the FDA's ongoing investigation of Avandia, agency officials appear to remain determined to turn a blind eye to the serious health risks associated with Avandia. In March 2006, an FDA drug safety supervisor approved a reviewer's recommendation of a black box warning for Avandia on the risk of swelling that could lead to heart failure. *See* Saul and

Harris, *Diabetes Drug Still Has Heart Attack Risk, Doctors Warn*, N.Y. Times, June 6, 2007. But the supervisor reported that FDA officials overruled her decision, ordered her to retract her approval of the black box warning, and removed her from future supervisory reviews of Avandia. *Id.*

The FDA's approval of Ketek and Avandia should give the Court serious pause when considering the health and safety implications of Petitioner's and its *amici*'s sweeping preemption arguments. In both cases, the FDA pushed the drugs through to marketing approval despite an absence of reliable evidence of long-term safety and efficacy. Both cases also reveal FDA officials' willingness to ignore agency professionals in their determination to bring drugs to market or to keep them on the market, as both Ketek and Avandia are to this day. In light of these and other examples of the FDA's failure or inability to ensure the safety and efficacy of prescription drugs, the Court should reject the arguments for preempting application of state tort law to approved prescription drugs as contrary to the public health and safety concerns that underpin the FDCA itself.

II. THE FDA's INABILITY TO PREVENT OFF-LABEL PROMOTION OF PRESCRIPTION DRUGS FURTHER SHOWS THE AGENCY'S FAILURE TO ENSURE DRUG SAFETY AND EFFICACY.

The FDA also has failed to ensure prescription drug safety and efficacy through its regulation of

post-approval marketing. The FDCA and the FDA's implementing regulations prohibit manufacturers from marketing or promoting prescription drugs for "off-label" uses not approved by the FDA. *See* 21 U.S.C. § 331(a) and (d); 21 C.F.R. § 202.1(e)(4). This prohibition serves important safety-related purposes that implicate the effectiveness of the FDA's entire prescription drug approval system. As one commentator explains:

> [O]ff-label use has potentially negative consequences. It undercuts expectations that drug safety and efficacy have been fully evaluated. When newer, more expensive drugs are used off-label, it increases health care costs. It undermines the incentives for manufacturers to perform rigorous studies – and instead subtly encourages them to game the system by seeking approval for secondary indications for which clinical trials are less complicated and less expensive. And off-label use may discourage evidence-based practice.

Stafford, *Regulating Off-Label Drug Use – Rethinking the Role of the FDA*, 358 N. ENG. J. MED. 1427, 1427-28 (April 3, 2008). The off-label marketing ban is thus an important drug safety measure because it prevents manufacturers from promoting drug uses that are unsupported by evidence of efficacy that the FDA would require to overcome known and unknown health and safety risks.

Despite the off-label marketing ban's importance to the FDA's regulatory regime, the agency's failure to

enforce this prohibition is widely recognized as a systemic problem. The Government Accountability Office's recent study, *Prescription Drugs: FDA's Oversight of the Promotion of Drugs for Off-Label Uses*, GAO-08-835 (July 2008), concluded that:

- As of March 2008, the FDA's Division of Drug Marketing, Advertising, and Communications ("DDMAC") had the equivalent of 44 full-time staff devoted to overseeing all prescription drug promotion (*id.* at 9);
- during the calendar years 2003 through 2007, DDMAC received approximately 277,000 final promotional materials from drug companies, including 68,000 in 2007 alone (*id.* at 15-16);
- DDMAC lacks a system or process to consistently track its receipt and review of submitted promotional materials; (*id.*);
- the FDA has no separate oversight activities designed specifically for off-label promotion (*id.* at 5); and that
- the FDA itself acknowledges that it can only review a small portion of submitted promotional materials (*id.* at 13).

In light of these limitations on the FDA's ability to regulate off-label prescription drug use, it is hardly surprising that a commentator recently found that, "more and more frequently, *it is not FDA action but litigation that raises important questions about*

off label drug prescribing." Stafford, *supra*, at 1428 (emphasis added). The antipsychotic drug Zyprexa and the epilepsy drug Neurontin represent two such instances where private litigation brought to light promotion of off-label uses for prescription drugs with significant public health implications.

First, evidence showing promotion of the antipsychotic drug Zyprexa for off-label uses came to light through private tort and state Medicaid litigation over the drug's association with diabetes, hyperglycemia, and excessive weight gain. The FDA approved Zyprexa in 1996 for treatment of adults with schizophrenia and bipolar disorder. *See In re Zyprexa*, 489 F. Supp. 2d at 248. Over the next decade, Zyprexa was prescribed to approximately 20 million patients worldwide. *See* Berenson, *Drug Files Show Maker Promoted Unapproved Use*, N.Y. Times, Dec. 18, 2006. Between 1999 and 2002 alone, Zyprexa's sales revenues doubled from $1.5 billion to $3 billion. *Id.* During this time, the American Diabetes Association and other public health groups demonstrated that there was considerable evidence linking treatment with atypical antipsychotics such as Zyprexa to increased risk of diabetes and hyperglycemia and rapid increase in body weight. *See In re Zyprexa*, 489 F. Supp. 2d at 249-50.[4]

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[4] The FDA first required a package insert warning about risk of diabetes and hyperglycemia in late 2003. *Id.* at 248, but did not address changes to the warning label itself until 2007, four or more years after Japanese, European, Australian, and Canadian regulators required similar label warnings. *Id.* at 250-51.

As a result of tort litigation brought by Zyprexa patients and state Medicaid reimbursement litigation, it was discovered that Zyprexa's manufacturer engaged in a multi-year promotional campaign involving off label uses of the drug. As part of its "*Viva Zyprexa*" campaign starting in late 2000, the manufacturer identified *primary care* doctors as a market for prescribing Zyprexa, notwithstanding the fact that its only two approved uses (schizophrenia and bipolar disorder) are treated primarily by *psychiatrists*. *See* Berenson, *Drug Files*, *supra*. In 2003, despite the fact that the drug's approval was limited to treatment of adult schizophrenia and bipolar disorder, an executive vice president issued a message proclaiming that Zyprexa was "getting traction with some neurologists for treatment of pain," and that "we must seize the opportunity to expand our work with Zyprexa in the child-adolescent population." *See* Berenson, *Lilly E-mail Discussed Off-Label Drug Use*, N.Y. Times, March 14, 2008.[4] Both of these were off label uses for which there was no showing of effectiveness to the FDA that could even conceivably justify approval in the face of the health risks associated with Zyprexa. *Cf.* Kruszewski and Paczynski, *Atypical Antipsychotic Agents for the Schizophrenia Prodome: Not a Clear First Choice*, 20 INT'L J. OF RISK

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[4] This information came to light in a lawsuit filed by the State of Alaska seeking to recover from the manufacturer the Medicaid costs the state paid for treating Zyprexa patients who developed diabetes. *Id.*

& SAFETY IN MED. 37 (May 2008) (noting paucity of evidence supporting use for adolescents and young adults).

A second case in which privately initiated litigation exposed even greater evidence of promotion for off-label uses involved the epilepsy drug Neurontin. The FDA approved Neurontin in 1993 solely for combination use with other drugs to control epileptic seizures. *See Drugmaker to Pay $430 Million in Fine, Civil Damages*, FDA Consumer (July-Aug. 2004) (hereafter, "*Drugmaker to Pay*"). Dr. David Franklin worked as a "medical liaison" for Neurontin's manufacturer, the Parke-Davis division of Warner-Lambert Co., for five months in 1996 during which company officials trained him and other liaisons to promote various off-label uses at daily dosages that more than doubled the maximum dosage approved by the FDA. *See United States ex rel. Franklin v. Parke-Davis, Div. of Warner-Lambert Co.*, 147 F. Supp. 2d 39, 45-46 (D. Mass. 2001). In August 1996, after he left Parke-Davis, Dr. Franklin filed a nine-count *qui tam* complaint alleging that Parke-Davis engaged in a fraudulent scheme to promote sales of Neurontin for off-label uses, resulting in submissions of false claims to the Veterans Administration and for Medicaid reimbursement that disguised off-label uses as approved. *Id.* at 43. The United States joined the action as *amicus curiae*, *id.* at 46, and Dr. Franklin's claims survived a motion for summary judgment. *See United States ex rel. Franklin v. Parke-Davis, Div. of*

Warner-Lambert Co., 2003 U.S. Dist. LEXIS 15754 (D. Mass. Aug. 22, 2003).

The United States also launched a criminal investigation based on Dr. Franklin's allegations, and concluded that Warner-Lambert was promoting Neurontin for the off-label treatment of bipolar disorder, pain disorders, Lou Gehrig's disease, attention-deficit disorder, migraines, drug and alcohol withdrawal seizures, and restless leg syndrome, as well as for first-line monotherapy treatment of epilepsy. *See Drugmaker to Pay*, *supra*. Prosecutors further alleged that Warner-Lambert encouraged sales representatives to mislead doctors about the scope of Neurontin's FDA approval, the drug's efficacy, and about their own scientific credentials. *Id.* The government also alleged that Warner-Lambert paid physicians to allow sales representatives to accompany them to see patients, and offer patients treatment advice favoring use of Neurontin. *Id.* As a result of Dr. Franklin's *qui tam* action and the criminal investigation that it sparked, Warner-Lambert pled guilty to two counts of misbranding under the FDCA, paid a $240 million criminal fine and $83.6 million in civil damages, and paid $38 million in additional damages to the 50 states. *Id.*

The Zyprexa and Neurontin cases bear out the earlier-discussed criticism that, "more and more frequently, it is not FDA action but litigation that raises important questions about off-label drug prescribing." Stafford, *supra*, at 1428. In both cases, it was not FDA officials charged with enforcing the

statutory and regulatory ban on promoting off-label uses, but private and state government litigants who brought to light serious evidence of off-label prescription drug promotion. In the case of Zyprexa, this evidence came to light after the drug had been prescribed to tens of millions of users worldwide and was linked with development of diabetes and rapid weight gain.

The critical role that private litigation has played in uncovering and policing off-label prescription drug promotion only further counsels against adoption of Petitioner's and its *amici*'s sweeping arguments for preempting state tort law. Given the FDA's failure and inability to enforce this critical component of the regulatory system for ensuring prescription drug safety and efficacy, the Court should reject these preemption arguments as contrary to the public health and safety goals of the FDCA itself.

CONCLUSION

For the reasons set forth herein, the Vermont Supreme Court's decision rejecting Petitioner's pre-emption defense should be affirmed.

Respectfully submitted,

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IN THE

Supreme Court of the United States

WYETH,

Petitioner,

v.

DIANA LEVINE,

Respondent.

On Writ of Certiorari
to the Supreme Court of Vermont

BRIEF AMICUS CURIAE OF THE SENIOR CITIZENS LEAGUE IN SUPPORT OF RESPONDENT

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INTEREST OF AMICUS CURIAE[1]

The Senior Citizens League ("TSCL") is a registered d/b/a of TREA Senior Citizens League, a nonprofit, non-partisan social welfare organization, interested in the proper construction and application of the Constitution and laws of the United States. TSCL is incorporated under the laws of Colorado, and is tax-exempt under Section 501(c)(4) of the Internal Revenue Code of 1986. Headquartered in Alexandria, Virginia, TSCL is one of the nation's largest nonpartisan seniors groups, with more than 750,000 senior citizen members and supporters, engaging in education and advocacy. Its mission is to educate the public and alert senior citizens about their rights and freedoms as U.S. citizens, to assist members and supporters regarding those rights, and to protect and defend the benefits senior citizens have earned. It monitors developments in the United States with respect to the interests of senior citizens, defends those interests before government, and develops educational materials designed to explain to seniors their rights as U.S. citizens. This brief is part of TSCL's "Seniors Health Initiative," a multi-faceted program defending seniors' health rights. Although TSCL has no affiliation with the parties in this case, TSCL and its supporters may be directly impacted by this Court's resolution of the issue in this case, which concerns a claim of implied federal preemption by the petitioner that could extinguish a civil liberty long enjoyed by seniors and others.

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[1] The parties have filed blanket consents to the filing of amicus briefs. No counsel for a party authored this brief in whole or in part, and no person other than the *amicus curiae*, its members, or its counsel made a monetary contribution to its preparation or submission.

SUMMARY OF ARGUMENT

Petitioner Wyeth seeks a ruling from this Court that compliance with the drug labeling requirements of the Food and Drug Administration ("FDA") would impliedly preempt respondent Diana Levine's common law failure-to-warn tort claim. Wyeth's preemption claim is predicated on the mistaken view that among the powers granted to Congress is the power to protect the public health, safety and welfare, whereas, in fact, Congress enacted the Food, Drug and Cosmetics Act ("FDCA") pursuant to its power to regulate interstate commerce. By its misstatement of Congressional authority, Wyeth sidesteps the presumption against preemption of the police powers reserved to the states, as secured by the Tenth Amendment.

Additionally, Wyeth's preemption claim, if sustained, would deprive Diana Levine of her civil liberty, as secured both by the Tenth Amendment's reservation to the people of those powers not delegated to the federal government, and by Article I, Section 4, of the Vermont Constitution, which protects her right to seek a legal remedy for an injury done to her person and property. Wyeth's attempt to impute to Congress an intent to take away Ms. Levine's remedy by "due course of law" would, if sustained, violate the laws of nature, in derogation of the very nature of legislative power vested in Congress by Article I, Section 1, of the Constitution and in violation of this nation's commitment to a government of laws, not of men, as stated by Chief Justice John Marshall in Marbury v. Madison.

In its attempt to gain immunity from liability for its own negligence, Wyeth would ask this Court to disregard the benefits of state law in protecting consumers and assisting the work of the FDA. Unless supplemented by state tort law, the FDA statutory mission of drug approval and oversight sacrifices the health and safety of individual patients for the purported greatest good for the greatest number of people. Premarketing approval of drugs by the FDA is an important step in the process intended to prevent the marketing of certain potentially dangerous items, but the FDA approval and monitoring process cannot replace the comprehensive safety incentives, information disclosure, and victim compensation obtained from state liability law, as the FDA historically has acknowledged.

Moreover, even in the words of the recent report of one of its own advisory groups, the FDA's scientific expertise applied to the drug approval and oversight process is insufficient to protect the public health. According to the FDA Science and Mission at Risk Report, dated November 2007, "science at the FDA is in a precarious position: the Agency suffers from serious scientific deficiencies and is not positioned to meet current or emerging regulatory responsibilities." Indeed, the Report concluded that the FDA's evaluation methods employed in the new drug approval process have not kept up with scientific advances, thus putting "American lives at risk."

Clearly, carving out a new doctrine of FDA preemption insulating drug companies from failure to warn the public adequately of risks of which the drug companies are most knowledgeable would be contrary

to both sound legal reasoning and the interests of all who depend upon the civil rights and remedies that are the bedrock of our society and government.

ARGUMENT

I. PREEMPTING RESPONDENT'S COMMON LAW TORT CLAIM WOULD DEPRIVE HER RIGHT TO A REMEDY BY "DUE COURSE OF LAW" SECURED BY THE TENTH AMENDMENT TO THE U.S. CONSTITUTION AND ARTICLE I, SECTION 4, OF THE VERMONT CONSTITUTION.

Even though the basic question before this Court is one of statutory interpretation, it cannot be addressed properly without first placing the subject matter at issue in its appropriate constitutional context. Certain preemption cases involve powers delegated by the Constitution exclusively to Congress, such as "the conduct of [the nation's] affairs with foreign sovereignties[,] [where] [o]ur system of government is such that the interest of the cities, counties and states, no less than the interest of the people of the whole nation, imperatively requires that federal power in the field affecting foreign relations be left entirely free from local interference." Hines v. Davidowitz, 312 U.S. 52, 63 (1941). Other preemption contests involve "the historic police powers of the States" that are presumed "not to be superseded by [a] Federal Act unless that was the clear and manifest purpose of Congress" pursuant to the exercise of a power "clear[ly]" "in the federal domain." Rice v. Santa Fe Elevator Corp., 331 U.S. 218, 229-30 (1947).

This case — involving the health, safety, and welfare of the people of Vermont — clearly falls into the latter category, not the former. *See e.g.*, Whalen v. Roe, 429 U.S. 589, 603 n.30 (1977) ("It is well settled that the State has broad police powers in regulating the administration of drugs by the health profession."). Yet, both Petitioner Wyeth, and the Solicitor General in his amicus brief, treat the preemption issue in this case as if the federal government has plenary authority over the "public health," as it does over "foreign relations." Both place heavy reliance upon Hines for the proposition that Respondent Diana Levine's claim for compensation arising from Wyeth's failure to warn of the safety risks of its drug, Phenergan, "stands as an obstacle to the accomplishment and execution of the full purposes and objectives of" the Food, Drug and Cosmetics Act, 21 U.S.C. Sections 301, *et seq*. *See* Brief for Petitioner ("Pet. Br."), pp. 27, 40; Brief for the United States as Amicus Curiae Supporting Petitioner ("U.S. Br."), pp. 10, 24. Further, neither pays any attention to the constitutional authority upon which the FDCA actually rests, citing the Supremacy Clause as the only constitutional provision relevant to this case,[2] as if the states retain only those power crumbs that fall from the Congressional table.

Indeed, the Solicitor General makes the sweeping and indiscriminate claim that "the Supremacy Clause (U.S. Const. Art. VI, Cl. 2) [so] subordinates state law to federal law, [that] the courts should not lightly assume that federal law is so self-negating as to authorize state law to frustrate its objectives." *See*

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[2] *See* Pet. Br., pp. viii, 2; U.S. Br., pp. v., 30.

U.S. Br., p. 30. The Solicitor General errs, however, ignoring "the starting presumption that Congress does not intend to supplant state law." *See* New York State Conference of Blue Cross & Blue Shield Plans v. Travelers Ins. Co., 514 U.S. 645, 654 (1995). And Wyeth attempts to banish the presumption against preemption altogether, having relegated mention of it to a footnote near the end of its brief, fishing for support from United States v. Locke, 529 U.S. 89 (2000), wherein this Court refused to apply the presumption to a state regulation competing with a federal law "bear[ing] upon [the] national and international maritime commerce, [an] area [where] there is no beginning assumption that concurrent regulation by the State is a valid exercise of its police powers." *Id.*, 529 U.S. at 108.

Such is not the case with the issue of inadequate drug labels. Even before "the creation of the modern FDA in 1938, and its forerunner in 1908, there has been a steady stream of failure-to-warn litigation [based on state law] against drug companies." D. Vladeck, "Should Drug and Medical Device Regulation Bar State Liability Claims?" Testimony before the House Committee on Oversight and Government Reform, 110th Congress, p. 18 (May 14, 2008) ("Vladeck testimony"). And as Justice Ginsburg has documented in Riegel v. Medtronic, Inc., 552 U.S. ___, 169 L.Ed.2d 892 (2008), "state common-law claims for drug labeling and design defects [have] continued unabated despite nearly four decades of FDA regulation." *Id.*, 552 U.S. at ___, 169 L.Ed.2d at 913 (Ginsburg, J., dissenting). In view of this history, Wyeth's claim, if sustained, would be truly a radical departure from settled law.

A. Wyeth Has Failed to Overcome the Presumption Against Preemption of the Powers Reserved to the States.

Wyeth begins its argument with a citation to the Supremacy Clause in Article VI of the Constitution, stating "the Laws of the United States [shall be] the supreme Law of the Land." Pet. Br., p. 29. Conspicuously missing from its brief is any acknowledgment of the qualifying phrase that only those laws of the United States "which shall be made in Pursuance" of "[t]his Constitution" are supreme. *See* Article VI, Clause 2, U.S. Constitution. Also missing is any recognition of the Tenth Amendment's admonition that "the powers not delegated to the United States by the Constitution, nor prohibited by it to the states, are reserved to the states respectively, or to the people."

By divorcing the FDCA from its constitutional moorings, Wyeth is set free to paint with a broad brush the "full purposes and objectives of Congress" (Pet. Br., p. 29) to be the protection and promotion of the "public health" (*id.*, p. 7), as if Congress had plenary, rather than enumerated, legislative power, including the power to protect the health, safety, and welfare of the people. However, "[d]espite the vast reach of the federal taxing, spending, commerce and other powers, it remains true that these powers do not add up to a plenary law making authority, and Congress may still be found to have legislated beyond the 'necessary and proper' execution of its constitutional powers." H. Linde, "Without 'Due Process'" 49 Or. L. Rev. 125, 148-49 (1970). *See, e.g.*, United States v. Morrison, 529 U.S. 598 (2000) (federal

statute purporting to establish civil remedy for victims of gender-motivated violence not authorized under either Commerce Clause or 14th Amendment).

Thus, even today, Congress remains a legislature of enumerated powers. *See* U.S. Constitution, Article I, Section 1. And the power to protect and promote the "public health" is **not** one of them. To be sure, Congress does have the power "to **provide** for the General Welfare," but that power, as the Government conceded over 70 years ago, simply "qualifies the power 'to lay and collect taxes.'" *See* United States v. Butler, 297 U.S. 1, 64 (1936). Thus, the General Welfare Clause is not a grant of power at all; rather it, along with the Common Defense Clause, limits the grant of the power to tax, denying to Congress the use of its enumerated taxing power to expand the regulatory powers of Congress. *See* Butler, 297 U.S. at 68-72.

Since Congress has no power to regulate the health, safety, and welfare of the people, as such, it can only enact laws governing such matters as a "necessary and proper" **means** to the exercise of another power enumerated in the Constitution. *See* McCulloch v. Maryland, 17 U.S. (4 Wheat.) 316 (1819). In the case of food, drugs, and cosmetics, that enumerated power is the power "to regulate Commerce ... among the several States," as this Court ruled in Hipolite Egg Co. v. United States, 220 U.S. 45 (1911). Even Wyeth admits that the current FDA role under the FDCA is ultimately to determine whether a new drug should be approved, or an already approved drug should remain, in the stream of interstate commerce. *See, e.g.*, Pet. Br., p. 2, 5, 6, 30. *See also* 21 U.S.C. Section 331.

To be sure, part of FDA's task is to ensure that, before being distributed, a drug must meet certain safety and efficacy standards. Nonetheless, FDA's primary role is a market-regulating one, "requir[ing] premarket approval" before a drug may be introduced into interstate commerce, pursuant to a policy of "risk management," the centerpiece of which is the labeling of the drug with one eye on the health and safety of the consuming public, and the other eye on the successful marketing of the approved product. *See* Pet. Br., pp. 5-11. Indeed, FDA's mission is, first of all, "to promote the public health by **promptly and efficiently** reviewing clinical research and taking appropriate action on the **marketing** of regulated products in a **timely manner**," and secondly, to "protect the public health." *See* 21 U.S.C. Section 393(b)(1) and (2) (emphasis added).

In its brief, Wyeth is careful to camouflage its economic interests in marketing Phenergan as altruistic ones, once euphemistically stating that:

> In general, FDA regulation serves the dual objectives of protecting the public from dangerous products and promoting public health by **facilitating access to beneficial treatments.** [Pet. Br., p. 41 (emphasis added).]

Surely, FDA's approval of Phenergan, in Wyeth's eyes, not only "facilitated access to beneficial treatments," but also advanced the profitability of Wyeth. Indeed, "the right balance of warnings and instructions that promotes beneficial use of the drug while minimizing

associated risks"[3] at the same time increases the quantity of Phenergan sold. And any warning that might "'exaggerat[e] [a] risk [that] could discourage appropriate use of a beneficial drug'"[4] also would depress the market for Phenergan and lessen its profitability. Indeed, "in reality, there are few instances in which [any] company (which is trying to sell its drug) wants a *stronger* label than the FDA...." Kessler, D. and David Vladeck, "A Critical Examination of the FDA's Efforts To Preempt Failure-To-Warn Claims," 96 Geo.L.J. 461, 479 (2008) (hereafter "Kessler-Vladeck Article").

The Solicitor General, like Wyeth, is equally coy about Wyeth's economic interests in FDA labeling decisions. In his description of the FDA protective and promotional roles, he fails to acknowledge that the FDA's balancing of health risks and benefits impacts on Wyeth's balance sheet as well. For example, while he acknowledges that "[o]verwarning can ... deter beneficial uses of a drug," he does not go on to explain that such deterrence also can have an adverse impact on a drug's profitability. *See* U.S. Br., p. 19. As Aaron Kessleheim of the Harvard Medical School recently testified, "[m]anufacturers have a strong financial incentive to promote their drugs' effectiveness and increase sales of their products...." A. Kesselheim, M.D., J.D., "Should Drug and Medical Device Regulation Bar State Liability Claims?" Testimony before the House Committee on Oversight and

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[3] Pet. Br., p. 42.

[4] *Id.*

Government Reform, 110th Congress (May 14, 2008) p. 2.

The point here is not to fault Wyeth's efforts to make a profit, but to bring to the foreground that Wyeth's economic interests can influence the FDA's labeling/warning decision-making process and also drive its effort to bar access to the courthouse door to Ms. Levine. While Wyeth may obscure its economic interests, it cannot bury the fact that those interests played a key role in both the initial and ongoing FDA assessments of risk and efficacy, as well as in the ultimate labeling requirement of Phenergan. After all, the FDA's role was not an adversarial one. Rather, it was managerial — one in which the manufacturer and the FDA worked together to craft a mutually satisfactory label for the marketing of the drug. *See* Pet. Br., pp. 11-16. Thus, the label which emerged from the negotiations between Wyeth and the FDA was a label that satisfied the marketing interests of Wyeth together with the public health interests of the FDA. *See* Pet. Br., pp. 17-18.

This administrative process, whereby the regulated manufacturer jointly with the FDA agrees to the adequacy of a warning on its marketed product, gives rise to the real concern that, while the FDA is "ostensibly regulating [in] the 'public interest,' [that interest] is equated more and more with the interest of those being regulated." *See* B. Schwarz, Administrative Law § 1.11, p. 26 (2d Ed. Little Brown: 1984). FDA decisions are often "made by unelected and unaccountable agency officials — many of whom worked for drug and device companies before their government service and have returned or will return

via the revolving door to represent the same companies." Vladeck testimony, pp. 2-3. In any event, the managerial decision mutually agreed to by the FDA and Wyeth did not meet the **individual** safety and efficacy interests of Diana Levine. Nor did it meet her remedial interests to be compensated for an injury suffered as a consequence of the inadequacy of the FDA-approved label. That should come as no surprise, for completely missing from the FDCA is any remedial provision administering compensation for injuries that occur because the FDA erred in approving a label that did not adequately warn Ms. Levine and her physician of the risks of intravenous application of Phenergan by IV push. Indeed, "when the 1938 Act was being debated, Congress was told that the bill did not need to create a federal claim for damages because state law already permitted such actions to be brought." Vladeck testimony, p. 16. Seventy years later, there still is no such federal cause of action or other remedial measure.

As noted above, Wyeth and the Solicitor General rely heavily upon Hines (312 U.S. at 67), for their contention that Vermont tort law is preempted because it "stands as an obstacle to the accomplishment and execution of the full purposes and objectives of Congress." Pet. Br., pp. 27, 40, 41; U.S. Br., pp. 10, 24. However, the "purposes and objectives" of the FDCA do not "fully" protect the public health, in that the statute does not include compensation for injuries caused by faulty warning labels approved by the FDA.[5] This is due, in part, to the limited

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[5] When federal statutes nullify existing state damage claims "they do so in unmistakable terms and generally provide a federal

constitutional authority of Congress which must act only "within the sphere of delegated power," which, in turn, limits the preemptive effect of the federal enactment on state law. *See* Hines, 312 U.S. at 68 n.20.

The sphere of power delegated to Congress, and reflected in the FDCA, is interstate commerce, **not** the public health and safety. *See, e.g.*, 21 U.S.C. Section 331. Therefore, as a matter of constitutional law, Congress' concern for public health and safety is only a "necessary and proper" means to facilitate and protect the commercial interests of the nation, "preventing trade" in mislabeled, dangerous, and inefficacious drugs "between the states by denying to them the facilities of interstate commerce." *See* Hipolite Egg, 220 U.S. at 58. And, as was true of Congress' prohibition of the interstate transportation of lottery tickets, the FDCA's interdiction of such drugs that do not meet FDA's minimum standards of safety and efficacy is designed to "supplement,"[6] not to override, the state's common law tort system providing for compensation for persons injured by the wrongful conduct of another. For nearly 100 years, the two have co-existed, state tort law protected by the presumption against preemption. *See* Riegel v. Medtronic, 552 U.S. ___, ___, 169 L.Ed.2d 892, 913-14 (2008) and cases cited (Ginsburg, J., dissenting). Wyeth and the Solicitor General have not rebutted this presumption.

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remedy in lieu of displaced state remedies." Vladeck testimony, p. 9.

[6] *See* Champion v. Ames, 188 U.S. 321, 357 (1903).

B. Diana Levine's Exercise of Her Individual Right to a Remedy for Wyeth's Wrongful Action Is a Power Reserved to the People.

Not only does the presumption against preemption protect the "reserved" powers of the states to protect the health, safety, and welfare of their people, it also protects those powers that, by nature, belong to the people, as provided in the Tenth Amendment. As Joseph Story observed, those powers not invested in either the federal or state governments are "retained by the people, as part of their residuary sovereignty." 2 J. Story, Commentaries on the Constitution, Section 1907, p. 652 (5th ed., Little Brown: 1891). According to the nation's charter, it is the sovereign right of the people to constitute and to reconstitute their government so that their God-given rights to life, liberty, and the pursuit of happiness are secured. To that end, the people of each State and the people of the United States consented to their respective governments, distributing between them those powers that they saw fit, and prohibiting them from the exercise of powers that they believed unfit for a freedom-loving people.

Admitted in 1791 as the fourteenth state in the union, the people of Vermont did not delegate, nor had the people of the original 13 states so delegated, to the federal government any power to enact a general system of tort law. Rather, that was a power reserved to the State, just as it had been reserved to the original 13. Additionally, in 1786 before Vermont was admitted to the union, and again in 1793, the people of Vermont retained the right "to find a certain remedy, by having recourse to the laws, for all injuries or

wrongs which he may receive in his person, property or character." Vermont Constitution, Chapter 1, Article 4. *See* http://vermont-archives.org/govhistory/constitut/con93.htm. In reserving this right to the people, the people of Vermont followed in the footsteps of the people of Delaware. *See* Delaware Declaration of Rights, Section 12. *See also* Sources of Our Liberties, p. 339 (Rev. ed., R. Perry and J. Cooper eds.; ABA Foundation: 1978). And as former Oregon Supreme Court Justice Hans Linde has written, the Delaware Declaration spawned other comparable provisions, including Article I, Section 10 of the Oregon Constitution, all of which were:

> directed against the denial of a legal remedy to one who has a claim, arising from "injury done him in his person, property, or reputation".... For such a recognized legal injury, "every man shall have remedy by due course of law." [H. Linde, "Without 'Due Process,'" 49 Ore. L. Rev. 125, 136 (1970).]

This right to a remedy for wrong done is rooted in the "law of nature," namely, that every person has, by nature, "a particular right to seek reparation from" another who has damaged him in his person or property. J. Locke, The Second Treatise of Government, Chapter II. 10. Further, by that same law of nature, a civil magistrate cannot:

> by his own authority remit the satisfaction due to any private man for the damage he has received. That he who has suffered the damage has a right to demand in his own name, and he alone can remit; the damnified person has this power of

> appropriating to himself the goods or service of the offender by right of self-preservation. [*Id.*, Ch. II. 11.]

Aware of these Lockean principles, and considering themselves to have been in a "state of nature" in 1777-78, the people of Vermont "form[ed] a government best suited to secure their property, well being and happiness." *See* P. Gillies, "Not Quite a State of Nature: Derivations of Early Vermont Law," 23 Vt. L. Rev. 99, 99 n.1, 129-31 (Fall: 1998). Unlike her predecessor states, "Vermont had never been a crown colony, and it had never been recognized as a separate governmental entity by any state." Sources of Our Liberties, *supra*, p. 358. Exercising their "prerogatives of sovereignty," the people of Vermont constituted their government to enable themselves "to enjoy their natural rights, and the other blessings which the Author of existence has bestowed upon man." *Id.* at 362.

Two hundred and ten years later, the Vermont Supreme Court upheld one of these natural rights, ruling that any statute or rule, "must give way ... if its application would deprive [a] plaintiff ... of his constitutional right to a remedy under Chapter I, Article 4 of the Vermont Constitution." Lillicrap v. Martin, 156 Vt. 165, 177-78, 591 A.2d 41, 48 (1989). Thus, if this Court were to construe the FDCA to preempt Diana Levine's common law tort claim against Wyeth, it would be denying Vermont's constitutional guarantee of providing Diana Levine the opportunity to seek individual redress for an alleged legal wrong committed by Wyeth, Congress having provided no comparable remedy for such wrong. *See*

Sienkiewycz v. Dressell, 151 Vt. 421, 424-25, 561 A.2d 415, 424-25 (1989). Instead, this Court will have ruled that Congress intended to extinguish Diana Levine's individual tort claim to forward its purpose of having the public health protected by "having an expert agency balance drug risks and benefits,"[7] even at the price of Ms. Levine's amputated arm.

Such imputation of Congressional intent would violate the laws of nature upon which these United States were founded, in derogation of the very nature of legislative power vested in Congress by Article I, Section 1:

> [T]he law of nature stands as an eternal rule to all men, legislatures as well as others. The rules that they make for other men's actions must ... be conformable to the law of nature — i.e. the will of God, of which that is a declaration — and the fundamental law of nature being the preservation of mankind, no human sanction can be good, or valid against it. [J. Locke, 2d Treatise, Ch. XI. 135.]

Indeed, such a preemption decision would undercut one of the "chief ends" of civil government, namely, to counter weigh the ability of the powerful to escape their duty to make reparations for wrongs done to those less powerful. *See* J. Locke, 2d Treatise, Ch. IX. 123-131.

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[7] *See* Pet. Br., p. 24.

C. Depriving Diana Levine of her Common Law Right to a Remedy for Injury Caused by Wyeth Is Contrary to the Rule of Law.

Even the most careful search of the legislative powers vested in Congress by the Constitution reveals no enumerated power to deprive a person who has a common law right of "a legal remedy by suit or action at law, whenever that right is invaded."[8] As Chief Justice John Marshall stated in Marbury v. Madison, 5 U.S. (1 Cranch) 137 (1803):

> The very essence of civil liberty certainly consists in the right of **every individual** to claim the **protection of the laws**, whenever he receives an injury. One of the **first duties of government is to afford that protection**. [*Id.*, 5 U.S. at 163 (emphasis added).]

There is no question in this case that, according to the common law of Vermont, Diana Levine had a legal right not to lose her arm and her livelihood as a consequence of Wyeth's "fail[ure] to provide adequate warnings of the known dangers of injecting Phenergan directly into [her] vein." *See* Levine v. Wyeth, 944 A.2d 179, 182 (Vt. 2006). There is also no question that, if this common law right were preempted by the FDA's approval of the Phenergan label, then Diana Levine would have no remedy whatsoever for the legal wrong done by Wyeth to her person, her liberty, and her property, for she would be left with no legal recourse to right this egregious wrong.

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[8] *See* III W. Blackstone, Commentaries on the Laws of England, p. 23 (U. Chi. Facsimile ed.: 1768).

In his Commentaries on the Laws of England, Sir William Blackstone observed that "it is a settled and invariable principle in the laws of England, that **every right**, when withheld, **must have a remedy, and every injury its proper redress.**" III. W. Blackstone's Commentaries, p. 109 (emphasis added). And it was in response to this observation that Chief Justice Marshall wrote his now famous paean about the legal system of the newly formed United States of America:

> The government of the United States has been emphatically termed a government of laws, and not of men. It will certainly **cease** to deserve this high appellation, **if the laws furnish no remedy for the violation of a vested legal right.** [Marbury, 5 U.S. at 163 (emphasis added).]

Should this Court find that Congress, by enacting the Food, Drug and Cosmetic Act, has preempted the application of Vermont's common law of torts to the failure of Wyeth properly to warn Diana Levine and her physician of the dangers of the "IV-push" method of injecting Phenergan directly into her vein, then it would simultaneously be signing: (a) the death warrant to a government providing for individual redress according to the rule of law administered by a jury of one's peers; and (b) the birth certificate to a government providing for the collectivist good, according to the pragmatic opinion of scientists administered by unelected bureaucrats in Washington, D.C. *See* Pet. Br., pp. 2-4, 23, 24, 28-29, 40-41, 46 and 50-51.

This Court's preemption doctrine ought not be so construed and applied. To do so would transform a legal transgression into a "mere political act," the wrongful exercise of which would leave the "injured individual" with "no remedy." *See* Marbury, 5 U.S. at 164.

II. IN ITS DRIVE TO GAIN IMMUNITY FROM LIABILITY ARISING FROM ITS NEGLIGENCE, PETITIONER DISREGARDS THE BENEFITS OF THE STATE TORT LIABILITY SYSTEM IN PROTECTING CONSUMERS AND ASSISTING THE WORK OF THE FDA.

Petitioner asserts that the state tort system presents a "direct and positive conflict" with the FDA's role in regulating drug labeling. Pet. Br., pp. 51-54. However, rather than conflicting with the FDA labeling process, the state tort liability system for decades has complemented and assisted the FDA's role under FDCA. "For most of its seventy-seven year history, the Food and Drug Administration (FDA) has regulated the drugs sold in the United States without any significant interaction with the world of state-law damages litigation.... The agency's practice of non-participation in litigation was in keeping with the FDA's view that its regulatory efforts could comfortably coexist with state-law damage claims by consumers injured by drugs." Kessler-Vladeck Article, pp. 462-463.

This mutually-reinforcing relationship was described during the May 14, 2008 hearings held by the House Committee on Oversight and Government

Reform on "Should Drug and Medical Device Regulation Bar State Liability Claims?"[9]

At those hearings, former FDA Commissioner David A. Kessler, who served under both President George H.W. Bush and President William J. Clinton, cited in his written testimony a statement from the agency's chief counsel made in 1996 summarizing the FDA's position at that time, that Kessler said was applicable equally to both devices and drugs, and which is contrary to the position advanced by the government in this case[10]:

> FDA's view is that **FDA product approval** and **state tort liability** usually operate **independently**, each providing a significant yet distinct layer of consumer protection. FDA regulation of a device cannot anticipate and protect against all safety risks to individual consumers. Even the most thorough regulation of a product such as a critical medical device may fail to identify potential problems presented by the product. **Preemption of all such claims would result in the loss of a significant layer of consumer protection leaving consumers without a remedy** caused by defective medical devices. [D. Kessler, "Should Drug and Medical Device Regulation Bar State Liability Claims?" Testimony before the House Committee on

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[9] Copies of the witnesses' testimony, Chairman Waxman's Opening Statement, and a "Preliminary Hearing Transcript" are available at: http://oversight.house.gov/story.asp?ID=1943.

[10] *See* U.S. Br., pp. 10, 17-21.

Oversight and Government Reform, 110th Congress (May 14, 2008), p. 2 (emphasis added) ("Kessler testimony").]

Indeed, former Commissioner Kessler explained that it is "the manufacturers, not the Agency, that are in a far better position to know when a new risk emerges from a drug ... [a]nd it is the manufacturer that has the ability to make swift changes to a drug ... warning or product features. Doing away with the incentives to act responsibly and expeditiously to correct potential risks, incentives that are the result of state [tort] liability cases, would ... jeopardize the public's health." Kessler testimony, p. 8.

Georgetown University Law Center Professor of Law David C. Vladeck reinforced this view by explaining that "[s]tate liability litigation helps uncover and assess risks that are not apparent to the agency during a drug's approval process, and this 'feedback loop' enables the agency to better do its job." Vladeck testimony, p. 24. Vladeck observed that "[t]ime and again, failure-to-warn litigation has brought to light information that would not otherwise be available to FDA, to doctors, to other health care providers, and to consumers. And failure-to-warn litigation has often preceded and clearly influenced FDA decisions to modify labeling, and, at times, to withdraw drugs from the market." *Id.*, pp. 24-25.

In his Opening Statement to the May 2008 Oversight Committee hearings on FDA preemption, Committee Chairman Waxman explained how some profit-making pharmaceutical firms have operated, and how the public safety would be worsened by

federal preemption: "Some drug and device companies have hidden and manipulated important safety data ... failed to report serious adverse events ... [and] failed to disclose known defects. If manufacturers face no liability, all the financial incentives will point them in the wrong direction, and ... abusive practices will multiply." At that point "even if a company withholds information about potentially fatal defects from physicians, patients, or the FDA, it is still immune from liability...." H. Waxman, Chairman, Waxman Opening Statement, "Should Drug and Medical Device Regulation Bar State Liability Claims?" Hearing, House Committee on Oversight and Government Reform, 110th Congress (May 14, 2008), pp. 1-2.

As contrasted with the current system where federal regulation and state tort liability exist side by side, Chairman Waxman described the type of preemption claims made by the pharmaceutical industry as a "radical legal doctrine" under which "one of the most powerful incentives for safety — the threat of liability — would vanish." *Id.*, p. 1.

It is undisputed that the FDA, until relatively recently, espoused the view "that state tort law [does] not interfere with federal regulation" in the area of the FDA's drug labeling oversight, and that it was only in 2006, in finalizing a new regulation concerning a "Highlights" section on drug labels, that the FDA officially espoused a diametrically different view. Respondent's Brief in Opposition, pp. 8-9. And no persuasive reason has been offered for the FDA's about-face. In fact, in view of the FDA's own admitted concerns about its ability to keep abreast of scientific developments (*see* Section III, *infra*), the timing of the

FDA pronouncement could hardly be worse. Certainly, the argument against federal preemption with respect to pharmaceutical warnings neither advocates nor promotes agency inattention or inaction. Quite to the contrary, the FDA is integrally involved in approving every drug for marketing, and the FDA — by regulation — has a voice in the form and content of the drug label, as well.

But that is not to say that the FDA initiates label changes, or that it must approve any and all label changes before they are made. Even if the petitioner's argument that it could not have made a change to Phenergan's label without FDA approval (Pet. Br., pp. 34-40) were true[11], it is clear from the decision below, as well as from a reading of the relevant FDA regulations, that a drug manufacturer has the prerogative to initiate changes to a drug label's warning in the interest of public safety, and there is no evidence that, had it unilaterally initiated or made such a change with respect to Phenergan, it would have been subject to any adverse regulatory action as to liability for unauthorized distribution or misbranding. *See* Wyeth v. Levine, 944 A.2d at 185-86, 188-89; Resp. Br. 31-45. *See also* 21 C.F.R. § 314.70(c); Kessler-Vladeck Article, pp. 479-80.

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[11] This contention is certainly not uncontested. *See* Vladeck testimony, pp. 19-21.

III. THE FDA'S SCIENTIFIC EXPERTISE APPLIED TO THE DRUG APPROVAL AND OVERSIGHT PROCESS ALONE IS INSUFFICIENT TO PROTECT THE PUBLIC HEALTH.

Underlying the claim to FDA preemption is the assumption that the FDA drug approval process is scientifically sound, unbiased, and comprehensive — that it alone is sufficient to ensure a drug's safety and effectiveness. That assumption is false. According to a recent report by one of its own Advisory Boards, FDA scientific expertise is inadequate, placing the nation's health at risk. *See* FDA Science and Mission at Risk: Report of the Subcommittee on Science and Technology of the FDA's Science Board (November 2007) (hereinafter "FDA Science Report"), at 2-6.

On March 31, 2006, the FDA Commissioner requested his Advisory Board — the **Science Board** — to form a Subcommittee to conduct a broad review of FDA scientific capacities, processes and infrastructure which support FDA's core regulatory functions of pre-market review, product quality oversight, and post-market safety surveillance. The Science Board created a **Science and Technology Subcommittee**, instructing it to: (1) uncover "any important gaps in current scientific capacities"; (2) identify "areas of science" where the FDA should maintain, strengthen or refocus its efforts; (3) explore "opportunities ... to enhance overall effectiveness, [including] priority setting"; and (4) identify opportunities for "collaboration" to enhance FDA's scientific and technological capacities. FDA Notice,

"Request for Comments on the Science and Technology Report ...," 73 *Fed. Reg.* 869, at 870 (Jan. 4, 2008).

This charge culminated in the FDA Science Report of November 2007, and the Subcommittee's conclusion that "science at the FDA is in a precarious position: the Agency suffers from serious scientific deficiencies and is not positioned to meet current or emerging regulatory responsibilities." FDA Science Report, at 2. Indeed, the Report concluded that the FDA's "evaluation methods" employed in the new drug approval process have not kept up with "scientific advances," thus putting "American lives at risk." *Id.*[12]

The 2007 FDA Science Report also revealed that the FDA clearly overstated its scientific prowess in claiming that its scientific evaluations are authoritative, the 2007 Report having concluded, for example, (i) that "not only can the Agency not lead, it cannot even keep up with the advances in science" (FDA Science Report, at 3), (ii) that the "FDA cannot fulfill its surveillance mission because of inadequate staff and IT resources to implement cutting-edge

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[12] The FDA Subcommittee concluded that the FDA is in a precarious position based, *inter alia*, on the following specific findings: the FDA suffers from serious scientific deficiencies and is not positioned to meet current or emerging regulatory responsibilities (FDA Science Report, at 2); substantial weaknesses across the FDA (*id.*, at 3); the FDA can neither keep up with the advances of science nor fulfill its surveillance mission because of inadequate staff and IT resources (*id.*, at 3-4); and the FDA Information Technology infrastructure is obsolete, unstable, and lacks controls to execute effective disaster recovery protocols that ensure continuity of operations when systems are compromised (*id.*, at 5).

approaches to modeling, risk assessment and data analysis" (*id.* at 4), and (iii) that "scientific capabilities and capacity at the FDA overall are unevenly meeting current requirements, have areas of serious deficiencies and are not positioned to meet future needs." *Id.* at 20.

In sum, the FDA Science Report documents both that "the Agency ... is not positioned to meet current or emerging regulatory responsibilities" and that the FDA knows its processes are flawed. *Id.* at 2. However, those facts have not prompted the FDA to reexamine the foundation for its new preemption policy issued just the year prior to the FDA Science Report.

In justifying its claim for preemption, the FDA described itself as "the expert Federal public health agency charged by Congress with ensuring that drugs are safe and effective, and that their labeling adequately informs users of the risks and benefits of the product and is truthful and not misleading." *See* "Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products," 71 *Fed. Reg.* 3921, 3934 (Jan. 24, 2006). Dismissing the view of "many courts" that "supplementary state law serves as an appropriate source of supplementary safety regulation for drugs by encouraging or requiring manufacturers to disseminate risk information beyond that required by FDA," the FDA opined that "additional requirements for the disclosure of risk information are not necessarily more protective of patients." *Id.* at 3934-3935. Claiming that state law actions "threaten FDA's statutorily prescribed role as the expert Federal agency responsible for evaluating

and regulating drugs," the FDA argued that such actions "encourage, and in fact require, lay judges and juries to second-guess the assessment of benefits versus risks of a specific drug to the general public — the central role of the FDA — sometimes on behalf of a single individual or group of individuals." *Id.* at 3935. Particularly in light of the FDA's own deficiencies revealed in the FDA Science Report, the FDA wrongly has belittled the role of expert opinion in a typical state common law tort action, by its assertion of "second-guessing" by a "lay" judge or jury.

Indeed, the FDA Science Board's low appraisal of the quality of FDA science confirms that a grant of immunity to drug manufacturers from individual tort claims based upon state law would clearly be unjustified. Whether the FDA's inadequacies are based upon a lack of adequate financial resources, or upon lack of confidence in the quality of FDA scientific experts, it would be inconsistent with the FDCA and long-standing FDA policy, as well as misguided in consideration of public safety, to establish a policy of federal preemption, precluding individual law suits based upon the FDA's "scientific expertise," in the face of the FDA's own Science Report conceding, *inter alia*, that "[t]he development of medical products based on 'new science' cannot be adequately regulated by the FDA." FDA Science Report, at 49.

In 2006, the Institute of Medicine ("IOM") also reported that the FDA "lacks the resources needed to accomplish its large and complex mission today, let alone to position itself for an increasingly challenging future." Vladeck testimony, pp. 23-24. FDA's Office of Drug Safety, responsible for monitoring adverse events

associated with the 3,000 prescription drugs (and 11,000 drugs altogether) on the market, has about 100 professional employees. *Id.* *See also* FDA Science Report, at 30-33 (recommending that FDA should immediately implement the IOM recommendations for improving drug safety).

Former FDA Commissioner Kessler, in his May 2008 Oversight Committee testimony, summarized cogently some of the FDA's limitations regarding its monitoring of drug safety and the critical role state tort law plays in promoting public safety:

> [T]here are real limits imposed by the limited resources the agency has available. The case for preemption must be examined in light of a clear-eyed appraisal of the FDA's ability to assure the safety of the drugs being marketed in the United States ... and many worry that the FDA is not adequately monitoring the safety of drugs once they are on the market. The FDA has long been hamstrung by resource limitations.... [T]he tort system has historically provided a critical incentive to drug and device companies to disclose important information to physicians, patients, and the FDA about newly emerging risks. My greatest concern with preemption is that it would, I believe, dramatically reduce the incentives for manufacturers to act quickly and responsibly to detect, analyze, investigate, and take action on potentially serious and life threatening adverse reactions once a drug is on the market. [Kessler Testimony, pp. 6-7.]

Preemption of state tort liability in failure-to-warn cases against negligent drug manufacturers could be expected to do enormous damage to the health of all Americans, particularly in light of the scientific deficiencies of the FDA, as documented by its own Science Board.

CONCLUSION

For the foregoing reasons, the decision of the Supreme Court of Vermont should be affirmed.

Respectfully Submitted,

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v.

DIANA LEVINE,

Respondent.

On Writ of Certiorari
to the Vermont Supreme Court

BRIEF OF THE TEXAS MEDICAL ASSOCIATION, TEXAS MEDICAL LIABILITY TRUST, AND NORTH CAROLINA MEDICAL SOCIETY AS *AMICI CURIAE* IN SUPPORT OF RESPONDENT

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INTEREST OF *AMICI CURIAE*[1]

The Texas Medical Association ("TMA") is a medical professional membership association (an IRC section 501c6 Texas non-profit corporation) of over 43,000 physicians licensed by the State of Texas, medical residents and medical students. The interests that the Texas Medical Association seeks to protect through this lawsuit are germane to its organizational purpose. One mission of TMA—in fact, its primary mission—is to improve the health of all Texans by being an advocate for patients and the profession of medicine. By filing this brief, TMA is seeking to limit the adverse consequences for patients and physician defendants in medical professional liability litigation when the primary defendant is in fact the drug manufacturer.

The Texas Medical Liability Trust ("TMLT") is a not-for-profit health care liability claim trust owned by its physician policyholders. TMLT was created in 1979, as a result of a legislatively-recognized health care and medical malpractice crisis, to provide an affordable and stable source of professional liability insurance to Texas physicians. TMLT is an independent insurer writing professional liability policies for more than 14,000 Texas physicians and

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[1] Pursuant to Rule 37.6, *Amici Curiae* state that no counsel for a party authored this brief in whole or in part, and that no party or counsel for a party made a monetary contribution intended to fund this brief's preparation or submission. Each party has consented to the filing of this brief. The parties' letters of consent are filed with the Court.

health care providers. TMLT is extensively involved in underwriting and risk management matters for the health care industry, and this requires TMLT to maintain knowledge and expertise of insurance industry standards as well as jurisprudential standards that affect liability insurance procurement and costs in Texas. TMLT is vitally interested in the consistency and predictability of Texas state and federal courts' decision making in cases involving professional liability of physicians and health care providers.

The North Carolina Medical Society (the "Medical Society") is the largest physician organization in North Carolina. Originally founded in 1849, more than 150 years later, the Medical Society has approximately 11,000 members. The Medical Society unifies doctors across North Carolina in all specialties and work settings on issues related to, *inter alia*: the physician-patient relationship, health regulation, and patient safety. As the largest physician organization in North Carolina, the Medical Society devotes significant resources to advocating physician viewpoints in the public policy arena. Specifically, the Medical Society and its member physicians take an active role in issues addressed by private companies, institutions, and the state government and work to ensure that the views of the medical community are presented in an organized and effective fashion.

SUMMARY OF THE ARGUMENT

Federal preemption of liability of pharmaceutical manufacturers for labeling and warning issues would represent an unwarranted expansion of federal

regulatory authority into the healthcare system. Physicians have a vital interest in the delivery of quality patient care, and prescription medications are an important tool in the physician's arsenal of healthcare weapons. However, the medical and pharmaceutical communities operate in an environment in which critical checks and balances, developed over decades, maximize the quality of patient care and minimize untoward events. A policy that extends protection from legal oversight to a single member of the healthcare community would disrupt this fragile system.

First, the notion that the FDA alone can effectively monitor all pharmaceutical industry members and their products is unrealistic. Analyses by medical scientists and government reviewers corroborate that the FDA is lacking in more than one respect in its ability to police such a large and diverse industry. Post-marketing monitoring of drug safety is a well-documented weakness in an already overburdened regulatory scheme. The policy of the medical community should be to enhance every reasonable mechanism that results in a better informed patient and physician population and, thereby, greater patient safety.

Second, if manufacturers are insulated from liability, physicians may find themselves as the scapegoat for adverse drug events. Physicians who practice responsible medicine should not be faced with the potential imposition of liability merely for having prescribed an FDA-approved drug. This is particularly true in the instance of "unlabeled" uses of medications, which are tacitly supported by the pharmaceutical

industry and which often account for a large percentage of medication use and sales. It is unlikely that judicial adoption of preemption in favor of pharmaceutical manufacturers will result in the wholesale discontinuation of all lawsuits arising from the use of FDA-approved prescription medications. Rather, a likely consequence of preemption will be that patients are left with no option but to prosecute claims against their physicians.

Finally, the argument that overwarning would lead to underuse of medications has no support in the peer-reviewed medical journals or in actual practice. It is lack of knowledge and public misperception that most studies have indicated are responsible for underuse of appropriate drugs.

Shielding only one member of the healthcare industry from liability—the pharmaceutical manufacturer—is not equitable, just, or right. The welfare of the patients and equitable healthcare reform should be the primary goal of physicians, the pharmaceutical industry, and the FDA.

ARGUMENT

I. PLACING SOLE AUTHORITY FOR DRUG SAFETY IN THE FDA IS NOT IN THE BEST INTERESTS OF PATIENTS OR THE HEALTHCARE SYSTEM IN GENERAL

The FDA is comprised of intelligent, well-meaning scientists and other professionals who face an almost insurmountable task. However, the FDA arguably does not have the manpower, financial resources, or

statutory authority to adequately police the drug and device industry.[2] Further, FDA approval does not and cannot guarantee long-term drug or device safety, thus post-approval surveillance is important.[3] It is in the context of post-marketing safety surveillance that the FDA's regulatory competence has most frequently been challenged.

While some observers view initial FDA approval of a drug as setting minimum rather than absolute standards for safety and disclosure,[4] the more critical point of contention is the ability of the agency to vigilantly oversee the post-approval safety of drugs it regulates. An analysis of the FDA's ability to conduct post-marketing safety surveillance found serious flaws in the regulatory framework as well as practical limitations. This report, prepared by the General Accounting Office, states:

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[2] David A. Kessler & David C. Vladeck, *A Critical Examination of the FDA's Efforts to Preempt Failure-To-Warn Claims*, 96 Geo. L.J. 461, 465 n.12 (2008); Subcommittee on Science and Technology, *FDA Science and Mission at Risk* (2007), *available at* http://www.bespacific.com/mt/archives/016720.html (last visited August 13, 2008).

[3] Gregory D. Curfman, Stephen Morrissey & Jeffrey M. Drazen, *A Pivotal Medical-Device Case*, 358 New Eng. J. Med. 76, 77 (2008).

[4] Russell Korobkin, *Who Should Protect the Public? The Supreme Court and Medical Device Regulation*, 357 New Eng. J. Med. 1650, 1680 (2007).

> FDA lacks a clear and effective process for making decisions about, and providing management oversight of, postmarket drug safety issues. The process has been limited by a lack of clarity about how decisions are made and about organizational roles, insufficient oversight by management, and data constraints. We observed that there is a lack of criteria for determining what safety actions to take and when to take them. FDA faces data constraints that contribute to the difficulty in making postmarket safety decisions. For example, FDA relies on clinical trials, reports of adverse drug reactions, and studies following the use of drugs in ongoing medical care in order to evaluate safety concerns and support its decisions, but each type of data has weaknesses. FDA also lacks authority to require certain studies and has resource limitations for obtaining data.[5]

This analysis, rendered by an agency of the government empowered to make an objective assessment of agency capabilities, should give pause to persons whose true goal is the protection of the public welfare.

Medical commentators echo the sentiment that FDA approval does not and cannot provide an assurance of drug safety in the long term. One writer

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[5] U.S. Government Accountability Office, GAO-06-402, *Drug Safety: Improvement Needed in FDA's Postmarket Decision-making and Oversight Process* (2006), *available at* http://www.goa.gov/new.items/d06402.pdf (last visited August 13, 2008).

has opined that "the premarket approval process can offer, at best, only a modest assurance of long-term safety."[6] Another article in the Journal of the American Medical Association ("JAMA") concluded that "clinical trials and routine regulatory oversight as currently practiced often fail to uncover important adverse effects for widely marketed products."[7] Yet a third observer remarked that "[r]ecent history casts some doubt on the ability of the FDA alone to protect the public and, thus, on the wisdom of dispensing with tort law."[8] These scholars underscore a deficiency in

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[6] Lawrence O. Gostin, *The Deregulatory Effects of Preempting Tort Litigation: FDA Regulation of Medical Devices*, 299 J. Am. Med. Ass'n 2313, 2314 (2008). Gostin also cites to findings of the FDA Science Board ("the scientific demands on the Agency far exceed its capacity to respond. This imbalance is imposing a significant risk to the integrity of the ...regulatory system, and hence the safety of the public."); U.S. Food & Drug Administration, Subcommittee on Science & Technology, *FDA Science and Mission at Risk: Report of the Subcommittee on Science and Technology* (2007), available ~~at~~ http://www.bespacific.com/mt.archives/016720.html (last visited August 13, 2008). The commentary quotes from the report of the Institute of Medicine (FDA "lacks the resources needed to accomplish its large and complex mission today, let alone to position itself for an increasingly challenging future."); Committee on the Assessment of the US Drug Safety System, Board on Population Health and Public Health Practice, *The Future of Drug Safety: Promoting and Protecting the Health of the Public* (Alina Baciu, Kathleen Stratton & Sheila P. Burke eds., National Academies Press 2006).

[7] Aaron S. Kesselheim & Jerry Avorn, *The Role of Litigation in Defining Drug Risks*, 297 J. Am. Med. Ass'n 308, 311 (2007).

[8] Korobkin, *supra*, note 4, at 1680.

the FDA's ability to conduct critical post-marketing safety surveillance.

Another scenario in which FDA's regulatory capabilities have been challenged is the area of monitoring off-label promotion of pharmaceuticals. It has long been accepted that physicians "may prescribe [drugs] for uses or in treatment regimens or patient populations that are not in approved labeling."[9] The result is that a significant percentage of prescriptions are prescribed for "unlabeled" uses.[10] A concern for patient health arises when physicians are encouraged to prescribe drugs for unlabeled uses through the scientific and medical literature, the integrity of which is subject to question. The conundrum has been described by one commentator:

> The published literature in medicine—a highly formalized scientific discourse among professionals largely free of major financial conflicts of interest—is based fundamentally on trust. While peer review provides some

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[9] FDA Drug Bulletin, Vol. 12, No. 1 (April 1982) ("Such 'unapproved' or, more precisely, 'unlabeled' uses may be appropriate and rational in certain circumstances and may, in fact, reflect approaches to drug therapy that have been extensively reported in the medical literature.") (Attached as Appendix A).

[10] Randall S. Stafford, *Regulating Off-Label Drug Use – Rethinking the Role of the FDA*, 358 New Eng. J. Med. 1427, 1427 (2008); Tracy Hampton, *Experts Weigh in on Promotion, Prescription of Off-Label Drugs*, 297 J. Am. Med. Ass'n 683, 683 (2007).

> important safeguards, the system was not designed to manage major financial conflicts or to withstand the relentless promotion of commercial interests.[11]

FDA regulations concerning distribution of journal articles by pharmaceutical manufacturers traditionally have included two important quality control mechanisms: (1) advanced FDA review of the articles to be distributed and (2) promotion limited to uses for which the manufacturer was working toward FDA evaluation.[12]

The FDA recently announced new rules governing what the agency refers to as "Good Reprint Practices for the Distribution of Medical Journal Articles and Medical or Scientific Reference Publications on Unapproved New Uses of Approved Drugs and Approved or Cleared Medical Devices."[13] These guidelines are intended to provide rules that govern

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[11] Bruce M. Psaty & Wayne Ray, *FDA Guidance on Off-Label Promotion and the State of the Literature From Sponsors*, 299 J. Am. Med. Ass'n 1949, 1950 (2008), available at http://jama.ama-assn.org/cgi/content/full/299/16/1949 (last visited August 13, 2008).

[12] Stafford, *supra*, note 10, at 1428.

[13] U.S. Food & Drug Administration, *Guidance for Industry: Good Reprint Practices for the Distribution of Medical Journal Articles and Medical or Scientific Reference Publications on Unapproved New Uses of Approved Drugs and Approved or Cleared Medical Devices* (2008), available at http://www.fda.gov/oc/op/goodreprint.html (last visited August 13, 2008).

the manner in which the pharmaceutical industry may disseminate medical literature the subject of which is "off label" uses of drugs.

Medical commentators who have addressed the subject of so-called "off-label" promotion appear to agree that the new FDA guidelines heighten the potential for mischief in the distribution of information on "off-label" uses of drugs. One author, evaluating the new regulations in JAMA, noted that "there are major limitations in relying on sponsor-distributed literature to regulate off-label use, including the selective publication of studies, the systematic manipulation of the literature, the absence from the literature of critical data necessary for evaluating off-label use, and the potential for undermining the NDA review process."[14]

Another writer remarked that the new rules amount to a "backward shift" in FDA policy that "seems oddly incongruous with current pressures aimed at improving postmarketing drug evaluation."[15] Additionally, the author postulated that "[t]he FDA may be conceding to drug manufacturers the responsibility for regulating their own off-label marketing practices."[16] This possibility provides little comfort to physicians, who rely on information provided by industry to deliver high quality healthcare to their patients. Yet another observer concluded:

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[14] Psaty & Ray, *supra,* note 11, at 1949-51.

[15] Stafford, *supra,* note 10, at 1429.

[16] *Id.*

"The fundamental issue is that people are viewing reprints as science and they believe that science is objective, but industry uses research to advance marketing goals."[17] While the vast majority of information provided by the pharmaceutical industry is of excellent quality, there are notable examples in which unscrupulous behavior has overcome intellectual honesty.[18] Thus, physicians are often left on the horns of a dilemma: disregard information provided by industry that may be scientifically reliable, or rely upon such information at their peril. Neither alternative serves the best interests of the public, the medical profession, or the pharmaceutical industry.

Reasonable oversight of information disseminated by industry to the medical profession seems necessary, but this task may be beyond the capability of an agency whose resources are limited. A report was issued by the General Accounting Office in July 2008, which found serious deficiencies in the FDA's oversight of the promotion of drugs for off-label uses. The report concluded:

> FDA oversees drug promotion for off-label uses by reviewing promotional materials that drug companies submit to the agency. However, because FDA does not have separate oversight

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[17] Mike Mitka, *Critics Say FDA's Off-Label Guidance Allows Marketing Disguised as Science*, 299 J. Am. Med. Ass'n 1759, 1759 (2008).

[18] Tracy Hampton, *Experts Weigh in on Promotion, Prescription of Off-Label Drugs*, 297 J. Am. Med. Ass'n 683, 684 (2007).

activities to specifically capture off-label promotion, its oversight occurs within a broader process that targets a variety of promotional violations. Furthermore, FDA reports it is unable to review all submissions because of the volume of materials it receives and prioritizes its reviews in order to examine those with the greatest potential impact on human health. However, FDA does not prioritize its reviews in a systematic manner but rather relies on its staff to sort through large volumes of material and select submissions for review. FDA is also hampered by the lack of a system that consistently tracks the receipt and review of submitted materials. To address these shortcomings, GAO recommended in 2006 that FDA track which materials it has reviewed. FDA has not acted on this recommendation and still lacks a standardized tracking system to monitor its review efforts. GAO believes that this recommendation remains valid. In addition to its reviews, FDA conducts monitoring and surveillance to identify violations that would not be identified through its review of submitted material—for instance, discussions between doctors and sales representatives. These efforts are also limited because FDA cannot observe all off-label promotion activities as they can take many forms and occur in a myriad of places.[19]

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[19] U.S. Government Accountability Office, GAO-08-835, *Prescription Drugs: FDA's Oversight of the Promotion of Drugs for Off-Label Uses* (2008), *available at* http://www.goa.gov/new.items/d08835.pdf (last visited August 13, 2008).

It is apparent that "[t]he concern about how to view scientific literature disseminated by manufacturers with a marketing agenda is a legitimate one and will likely not go away" in the foreseeable future.[20] Physicians and, by extension, their patients, are vulnerable to being misinformed when the agency responsible for policing communications by and from pharmaceutical companies is understaffed and therefore unable to perform this critical task.

Thus, in both post-marketing safety surveillance and pharmaceutical company promotion of its products, the FDA arguably is incapable of effectively fulfilling its regulatory obligations. This observation is not a criticism of the individuals who work at the FDA or the fine work this agency is capable of doing, but rather, recognition that the pharmaceutical industry presents oversight challenges that would tax even the most well-equipped agency.

II. PHYSICIANS MUST CONSIDER THE IMPACT OF PREEMPTION ON THEIR PATIENT POPULATION AND THE MEDICAL COMMUNITY IN GENERAL

The physician-patient "relationship is based on trust and gives rise to a physician's ethical obligation to place patient's welfare above their own self-interest

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[20] Bruce Patsner, *Promotion of Off-Label Uses of Prescription Medical Products: FDA's Proposed New Guidance*, Health Law Perspectives (June 2008), available at: http://www.law.uh.edu/healthlaw/perspectives/homepage.asp (last visited August 13, 2008).

and above obligations to other groups and to advocate for their patients' welfare. A physician has a duty to use sound medical judgment, and to keep the best interests of the patient paramount."[21] As a member of the medical profession, a physician must recognize "responsibility to patients first and foremost, as well as to society, to other health professionals, and to self."[22]

Physicians must first consider the consequences to their patients of momentous public policy issues such as preemption. Articles in the leading journals in America have addressed the potential consequences of preemption on society. These authorities oppose any policy that would provide a blanket protection exclusively to drug and device companies without a corresponding right to seek legal redress.[23] A recent editorial in the Journal of the American Medical

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[21] Harris County Medical Society of Ethics, *Principles of Medical Ethics* (2001), *available at* http://hcms.org/Template.aspx?id=247 (last visited August 13, 2008).

[22] American Medical Association, *Principles of Medical Ethics* (2001), *available at* http://www.ama-assn.org/ama/pub/category/2512.html (last visited August 13, 2008), states:

> III. A physician shall respect the law and also recognize a responsibility to seek changes in those requirements which are contrary to the best interests of the patient.
>
> * * *
>
> VIII. A physician shall, while caring for a patient, regard responsibility to the patient as paramount.

[23] Curfman, *supra* note 3.

Association provided one view of the problem, focusing on the need to curb frivolous lawsuits, but recognizing the negative impact of preemption on the nation's problem of poorly defined or inadequately presented drug risk information.[24] This commentary recognizes that there are competing interests at work in the preemption debate.

A 2007 study examined the historical impact of the justice system on drug safety.[25] The article noted that this process serves a productive role in a complex intersection of the justice system, the regulatory apparatus, and science. Physicians do not condone unfounded legal claims or necessarily believe the tort system is the most efficient tool by which drug safety may be enhanced. Nonetheless, Amici disfavor a social policy in which patients injured by poorly designed—but FDA-approved—medical devices have no recourse.[26] Each of these problems deserves attention from the healthcare community, including the pharmaceutical community.

History shows that incidents do occur in which physicians prescribe and their patients are exposed to drugs and devices that result in avoidable harms. When untoward events occur and responsibility must be assessed, the interests of all participants in the

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[24] Kesselheim, *supra*, note 7.

[25] *Id.* at 309.

[26] *See* Leonard H. Glantz & George J. Annas, *The FDA, Preemption, and the Supreme Court*, 358 New Eng. J. Med. 1883, 1885 (2008).

healthcare community should be considered. Under the present scenario, however, the federal preemption doctrine focuses solely on protecting the interests of drug and device manufacturers. "The preemption doctrine plays a constructive role in the allocation of regulatory authority over national industries. But its purpose has never been to grant broad legal immunity to private industry."[27] It would be a disservice indeed if the party most responsible for the safety of drugs and devices were cloaked in a protective shield of preemption while healthcare providers and patients were left to fend for themselves.

The February 2, 2008 New England Journal of Medicine included an important editorial on this subject.[28] Although addressing the topic of preemption in the device setting, the policy issue reached is the same and the conclusion of the authors consistent:

> Ultimately, we believe that the pivotal question for the justices in *Riegel v. Medtronic* resides in what is in the best interest of American society. Is it in the people's interest to shield medical device companies from product-liability claims? Would such a decision benefit patients by making more lifesaving medical devices available, or would there be adverse effects on the overall safety of devices? Is the FDA premarketing approval process sufficiently rigorous and comprehensive to justify

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[27] *Id.*

[28] *Id.*

> immunization of the industry against tort claims? And if medical-device manufacturers are shielded from liability, what about drug manufacturers? Or would society be better served if patients retained their right to seek legal redress when they believed they had been damaged by a faulty medical device? In the long run, would this result in safer medical devices for patients?
>
> If Congress later concludes that the Supreme Court has come to the wrong conclusion — that is, a conclusion that is too restrictive of patients' legal prerogatives and does not serve the public interest — Congress can then act to clarify the law and leave open the possibility that patients injured by devices or drugs can seek legal redress.
>
> But by rejecting Medtronic's plea for immunity, the Supreme Court can act now to protect patients. From time to time, the Court agrees to hear a case that may have major, even momentous, implications for health care. *Riegel v. Medtronic* is such a case.[29]

These venerable authorities observe that the benefits of providing absolute immunity to drug and device manufacturers is outweighed by the harm to patients and the negative ramifications for physicians. More importantly the ethical creed by which physicians serve would be disrupted by a policy that placed the

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[29] Curfman, *supra*, note 3, at 77.

burden of regulatory, scientific, or corporate failures on the backs of individuals.

Most recently, the New England Journal of Medicine published a Perspective in its July 3, 2008 edition. The editorial unabashedly challenges the rationale for preemption and remarks that "Congress, not unelected appointees of a federal agency, has the power to decide whether preemption should apply."[30] Further, while "frivolous lawsuits should not be condoned," physicians must speak up against any policy decision that will "result in drugs and devices that are less safe and will thereby undermine a national effort to improve patient safety."[31] Finally, "[i]n stripping patients of their right to seek redress through due process of law, preemption of common-law tort actions is not only unjust, but will also result in the reduced safety of drugs and medical devices for the American people."[32]

There is a strong consensus in the medical community that the interests of patients demand respect and deserve protection. Physicians play a critical role in these tasks. Hence, there is a responsibility for ethical physicians to speak up when action is contemplated that disserves the interests of patients and the medical community at large.

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[30] Gregory D. Curfman, Stephen Morrissey & Jeffrey M. Drazen, *Why Doctors Should Worry About Preemption*, 359 New. Eng. J. Med. 1, 1 (2008).

[31] *Id.* at 2.

[32] *Id.* at 3.

III. PHYSICIANS SUPPORT HEALTHCARE REFORM MEASURES, BUT PIECEMEAL ADOPTION OF PREEMPTION IS NOT EQUITABLE

Physicians eschew any process that detracts from their goal of delivering high quality, economical healthcare to their patients. Tort litigation is an undesirable, but historical, component of the medical and justice systems in America. Physician organizations across the country lobby for tort reform that recognizes the interests of both physicians and patients. Physicians realize that unfortunate outcomes do occur, and the legal system plays an essential role in resolving disputes when they do arise. Nonetheless, the medical community does not favor, and in fact discourages, irresponsible lawsuits.

It is unlikely that the judicial adoption of preemption in favor of pharmaceutical manufacturers will end lawsuits arising from the use of FDA-approved drugs. One potential consequence of preemption would be that patients would be left with no option but to prosecute claims against their physicians.[33] This possible outcome would be unjust indeed.

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[33] *Id.* at 3; *see also* the Amicus Brief filed in *Riegel v. Medtronics* in which it is suggested that physicians may be vulnerable. *Riegel v. Medtronics* Amicus Br. 14, *available at* http://www.wlf.org/upload/RIEGEL-%20WLF%20Amicus%20Brief.pdf (last visited August 13, 2008).

A cogent example of the potential negative consequences of preemption for healthcare providers is found in the case at bar. Petitioner's brief contains a recitation of facts emphasizing that the healthcare provider committed two departures from the strict terms of the product labeling. Petitioner remarks that Ms. Levine's healthcare provider administered "double the labeled amount" of drug and thereafter took action "even though the labeling" instructed a different course of care. It is unfortunate that, in the pharmaceutical litigation setting, industry is often overcome with the temptation to attempt to shift responsibility to the healthcare provider for untoward results that inevitably occur. Left unanswered is the question of whether the healthcare provider was acting as a reasonable and prudent provider under the facts of the case. Further, it is critical to investigate whether the actions of the healthcare provider were known to industry to be the usual and customary procedures involving the subject drug.[34] In the context of preemption, these issues unfortunately would never merit attention.

Two recent mass tort litigations also provide evidence of the uncertainty that is fostered by the judicial adoption *vel non* of preemption. In the Vioxx

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[34] *See McNeil v. Wyeth*, 462 F.3d 364, 368 (5th Cir. 2006)) ("In sum, because the widespread long-term use of Reglan suggests that Wyeth's indication for use for not more than twelve weeks was widely disregarded, a jury could infer that the warning was ineffective and therefore inadequate. It follows that Wyeth had a duty, under Texas law, adequately to warn the learned intermediary of known risks with long term use and not to be misleading as to that risk.").

litigation, the presiding federal judge, the Honorable Eldon Fallon, not only ruled against the defendant drug company on the issue of preemption, he chastised the FDA for the manner in which it implemented its preemption policy.[35] Conversely, a Texas state court judge granted a drug company motion based on a confusing, multi-faceted argument that mixed state and federal preemption allegations.[36] In the hormone replacement therapy litigation, presiding Federal District Judge William Wilson denied a motion for relief based on preemption.[37] A Texas state court judge granted a motion in a hormone replacement case based on similar grounds, though no written opinion was issued.[38] These cases exemplify the difficulty and unpredictability in judicially adopting a controversial and potentially unwise policy such as preemption.

Another question that remains is whether physicians are entitled to the same shield of preemption as industry. By any application of principles of fairness and justice, healthcare providers

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[35] *In re Vioxx Prods. Liab. Litig.*, 501 F. Supp. 2d 776, 788 (E.D. La. July 3, 2007).

[36] *Ledbetter v. Merck & Co., Inc.*, Master Docket No. 2005-59499, 157th Judicial District Court of Harris County, Texas (no publication) (attached at Appendix B).

[37] *In re Prempro Prods. Liab. Litig.*, MDL Docket No. 4:03CV1507-WRW (E.D. Ark. June 15, 2006).

[38] *Susan Brockert, et al. v. Wyeth Pharmaceuticals, et al.*, Cause No. 2003-49357, In the 151st Judicial District Court of Harris County, Texas.

should receive the same measure of protection as drug companies if the physicians utilize or prescribe FDA-approved drugs in a reasonable and prudent manner.[39] Unfortunately, in the evolving common law environment, this issue is not presented to the court for decision.

The FDA and industry have also addressed this issue only minimally. The FDA preamble[40] is not explicit in the effect of preemption on doctors; the preamble includes this comment: "Preemption would include not only claims against manufacturers as described above, but also against health care practitioners for claims related to dissemination of risk information to patients beyond what is included in the

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[39] A Texas statute provides a rebuttable presumption that the defendants in a product liability action, including the health care provider, "are not liable with respect to the allegations involving failure to provide adequate warnings or information" if the warnings that accompanied the product "were those approved" by the FDA, but this presumption may be rebutted if the claimant establishes that the defendant "withheld from or misrepresented" to the FDA "required information" that was "causally related" to the claimant's injury. TEX. CIV. PRAC. & REM. CODE § 82.007(a) *et seq.* (Vernon 2003). Ironically, state statutes such as this may no longer have application if preemption forbids any type of state "requirements" concerning drug regulation or labeling.

[40] FDA, Final Rule, Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products, 71 Fed. Reg. 3992 (Jan. 24, 2006) (codified at 21 C.F.R. pts. 201, 314, 601).

labeling. (*See, e.g., Bowman v. Songer*, 820 P.2d 1110 (Col. 1991).)"[41]

One industry commentator has opined: "Notably, although FDA disclaims authority to regulate medical practice, consistent with its well-established policy of noninterference in the practice of medicine, the preamble twice makes clear that the FDA intends for its regulation of risk information for prescription drugs to shield health care practitioners from state-law claims."[42]

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[41] *Id.* at 3936. It is not clear why the FDA cites to *Bowman*. This lawsuit involved an allegation by the defendant physician that he was unfairly held to the standard of care of a drug manufacturer by introduction into evidence of the Physicians' Desk Reference. The court held:

> "In *Hamilton v. Hardy*, 37 Colo. App. 375, 380, 549 P.2d 1099, 1104 (1976), our court of appeals cited *Crouch v. Most*, 78 N. Mex. 406, 432 P.2d 250 (1967), in stating that 'a manufacturer's warnings do not set an absolute standard of care. . . . The standard by which a physician's conduct is judged is an objective community standard. Reliance solely on the manufacturer's warnings may or may not have been within the standard of medical practice in Denver at that time.' Thus, admission of the excerpt from the Physicians' Desk Reference was proper to aid the jury in determining whether Bowman's actions were consistent with the standard of care, and did not place upon him the product manufacturer's liability."

An adverse judgment against the physician was affirmed.

[42] Daniel E. Troy, *The Patient's Interest in FDA Preemption*, Ave Maria L. (forthcoming), *available at* http://www.federalismproject.org/preemption/papers/Troy_Patients_Interest_in_FDA_Preemption.pdf (last visited August 13, 2008).

Unfortunately, there is little certainty what the eventual impact of preemption may be on physicians in the tort litigation setting. The issue in the case at bar is clear however. Extending a shield of implied preemption to one member of the healthcare industry is not the solution. Physicians advocate the adoption of litigation reform measures that would serve the interests of all members of the healthcare community, not just the pharmaceutical industry.

IV. ONE KEY PREMISE UPON WHICH PREEMPTION IS BASED – CONCERNS ABOUT OVERWARNING – IS UNFOUNDED

One of the arguments presented in support of the adoption of preemption is that the current system fosters overwarning of drug risks. The available evidence does not support the conclusion that overwarning is precipitated by the legal system, but rather that inadequate use of drugs is more likely due to patient misperceptions and physicians' lack of knowledge about available drug treatments.

There is evidence that improvements can be made in various facets of medical care in the United States.[43] Preempting tort claims against drug manufacturers is not the panacea for the nation's ills. Rather, the medical community advocates broadscale and continuing improvement in areas in which it has been

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[43] *See, e.g.*, William H. Shrank, et al., *The Quality of Pharmacologic Care for Adults in the United States*, 44(10) Medical Care 936, 940 (2006).

proven to be justified: prescribing indicated medications, monitoring, education, and continuity of care.[44]

In conclusion, while all participants in the healthcare community should advocate the efficient and timely use of appropriate medical therapy, "overwarning" precipitated by tort litigation is not documented to be the primary cause of underuse of medications. The empirical data tends to show that increasing the knowledge of physicians and patients will result in improvement in prescribing habits and overall patient care. Hence, a concern of "overwarning" should not be relied upon as a basis for adopting preemption.

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[44] Takahiro Higashi, et al., *The Quality of Pharmacologic Care for Vulnerable Older Patients*, 140 Ann. Intern. Med. 714, 714-720 (2004). The article also cites to "possible reasons" for "the underuse of potentially beneficial medications," but fails to mention civil lawsuits as a reason for this deficiency. *See also* Elizabeth McGlynn, et al., *The Quality of Health Care Delivered to Adults in the United States*, 348 N. Eng. J. Med. 2635, 2635-45 (2003).

CONCLUSION

For these reasons, and those stated in Respondent's brief, the judgment of the Vermont Supreme Court should be affirmed.

Respectfully submitted,

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August 14, 2008

APPENDIX

APPENDIX A

FDA Drug Bulletin
April 1982
Volume 12 Number 1
Pages 4-5

Use of Approved Drugs for Unlabeled Indications

The appropriateness or the legality of prescribing approved drugs for uses not included in their official labeling is sometimes a cause of concern and confusion among practitioners.

Under the Federal Food, Drug, and Cosmetic (FD&C) Act, a drug approved for marketing may be labeled, promoted, and advertised by the manufacturer only for those uses for which the drug's safety and effectiveness have been established and which FDA has approved. These are commonly referred to as "approved uses." This means that adequate and well-controlled clinical trials have documented these uses, and the results of the trials have been reviewed and approved by FDA.

The FD&C Act does not, however, limit the manner in which a physician may use an approved drug. Once a product has been approved for marketing, a physician may prescribe it for uses or in treatment regimens or patient populations that are not included in approved labeling. Such "unapproved" or, more

precisely, "unlabeled" uses may be appropriate and rational in certain circumstances, and may, in fact, reflect approaches to drug therapy that have been extensively reported in medical literature.

The term "unapproved uses" is, to some extent, misleading. It includes a variety of situations ranging from unstudied to thoroughly investigated drug uses. Valid new uses for drugs already on the market are often first discovered through serendipitous observations and therapeutic innovations, subsequently confirmed by well-planned and executed clinical investigations. Before such advances can be added to the approved labeling, however, data substantiating the effectiveness of a new use or regimen must be submitted by the manufacturer to FDA for evaluation. This may take time and, without the initiative of the drug manufacturer whose product is involved, may never occur. For that reason, accepted medical practice often includes drug use that is not reflected in approved drug labeling.

With respect to its role in medical practice, the package insert is informational only. FDA tries to assure that prescription drug information in the package insert accurately and fully reflects the data on safety and effectiveness on which drug approval is based.

APPENDIX B

MASTER DOCKET NO. 2005-59499

**IN THE DISTRICT COURT OF
HARRIS COUNTY, TEXAS
157th JUDICIAL DISTRICT**

**(Trial Court: 151st Dist. Court of
Harris County, Cause No. 2005-58543)**

[Filed April 20, 2007]

Ruby Ledbetter	)
	)
v.	)
	)
Merck & Co., Inc.	)
	)

**Order Granting Defendant's Motion
for Partial Summary Judgment
And Granting Expedited Appeal**

Defendant Merck & Co., Inc. ("Merck") has filed a no evidence motion for partial summary judgment on plaintiff's warning claims. This motion is based on a 2003 Texas statute governing FDA approved warnings. TEX. CIV. PRAC. & REM. CODE ANN. §82.007. Merck argues that §82.007 is preempted by federal law. For reasons stated, the motion is granted.

1. Background

Vioxx (known generically as rofecoxib) is a NSAID (non-steroidal anti-inflammatory drug). This class of drugs includes over the counter medications, such as Advil (ibuprofen) and Aleve (naproxen) and a variety of prescription medicines. NSAIDS work by inhibiting cyclooxygenase (COX), an enzyme that stimulates synthesis of prostaglandins, which are chemicals produced in the body that promote certain effects.

In the early 1990s, scientists discovered that the COX enzyme was composed of two forms. COX-1 affects the synthesis or production of prostaglandins responsible for protection of the stomach lining; COX-2 stimulates the prostaglandins that cause pain and inflammation. This belief led to the hypothesis that a selective NSAID, designed to inhibit COX-2, but not COX-1, could offer pain relief without the risk of fatal or debilitating gastrointestinal perforations and ulcers. This led Merck to begin the development of such a drug, which became known as a COX-2 inhibitor. Vioxx is a COX-2 inhibitor.

In December 1994, Merck submitted an Investigational New Drug Application to the FDA seeking approval to conduct studies to test the safety of Vioxx to treat osteoarthritis, rheumatoid arthritis, and pain. In November 1998 Merck submitted a New Drug Application for Vioxx. The FDA reviewed the Merck submission and, as well, convened an Advisory Committee to review the data and make recommendations. On May 20, 1999, the FDA approved Vioxx for sale in the United States.

Vioxx was subjected to a number of studies and trials, including VIGOR, APPROVe, and others. APPROVe was a randomized clinical trial that compared Vioxx to a placebo. The APPROVe study indicated that the use of Vioxx increased the risk of cardiovascular thrombotic events such as myocardial infarctions.

On September 30, 2004, Merck withdrew Vioxx from the market. Thousands of lawsuits ensued across the country. On September 6, 2005, Texas cases were consolidated into this MDL, proceeding. There are currently over 1,000 Vioxx cases in these consolidated Texas proceedings; virtually all of them contain an allegation that Merck failed to provide an adequate warning.

2. Preemption

A. The Texas Act

In 2003, the Texas legislature enacted TEX. CIV. PRAC. & REM. CODE ANN. §82.007, which provides, in part:

> **§ 82.007. Medicines**
>
> (a) In a products liability action alleging that an injury was caused by a failure to provide adequate warnings or information with regard to a pharmaceutical product, there is a rebuttable presumption that the defendant or defendants, including a health care provider, manufacturer, distributor, and prescriber, are not liable with respect to the allegations

involving failure to provide adequate warnings or information if:

> (1) the warnings or information that accompanied the product in its distribution were those approved by the United States Food and Drug Administration for a product approved under the Federal Food, Drug, and Cosmetic Act (21 U.S.C. Section 301 et seq.), as amended, or Section 351, Public Health Service Act (42 U.S.C. Section 262), as amended; or

* * * *

(b) The claimant may rebut the presumption in Subsection (a) as to each defendant by establishing that:

> (1) the defendant, before or after pre-market approval or licensing of the product, withheld from or misrepresented to the United States Food and Drug Administration required information that was material and relevant to the performance of the product and was causally related to the claimant's injury;

* * * *

TEX. CIV. PRAC. & REM. CODE ANN. §82.007 (hereinafter the "Texas Act"). The Texas Act was one of a number of enactments in 2003 designed to achieve "tort reform" as a result of a perceived lawsuit crisis,

particularly involving the medical arena. This statute has yet to be construed by Texas appellate courts.

There is no question but that the FDA approved the general warnings or information provided by Merck with respect to Vioxx. Plaintiffs rely exclusively upon subsection (b)(1) of the Texas Act in order to rebut the Act's presumption that Merck is not liable for failure to provide an adequate warning.

B. Construction of the Texas Act.

In order to determine whether the Texas Act has been preempted, this Court must first construe the various terms contained in the Act.

1. Burden of Proof.

A threshold question confronting this Court concerns the burden of proof under the Texas Act. Section 82.007 states that a claimant may rebut the presumption in the statute by "establishing" that certain required information was withheld. What does "establish" mean? Merck equates "establish" with "prove" and argues that plaintiffs must prove that such information was withheld or misrepresented by a preponderance of the evidence. Plaintiffs argue that the presumption "bursts" merely upon presenting some evidence that information was withheld. Thus, according to plaintiffs, at the conclusion of plaintiffs' case, the Court would rule as a matter of law whether some evidence of withholding or misrepresentation of evidence was presented, and thereafter, the failure to warn question would be presented to the jury.

Plaintiffs therefore argue that the court, rather than the jury, decides whether information was withheld.

The Court agrees with Merck. Plaintiffs have the burden to "establish" or prove that required information was withheld from or misrepresented to the FDA by a preponderance of the evidence. This is ordinarily a question for the jury.

2. Required Information

To rebut the presumption, plaintiffs must show that "required information" was withheld or misrepresented. "Required information" means that information which is required to be submitted to the FDA pursuant to federal statute and regulations governing pharmaceutical products.

3. Material Information.

The Texas Act next requires that claimants prove that "material and relevant" information was withheld. Not surprisingly, the parties presented two different definitions of materiality.

- Plaintiffs posit that they must merely show "that the allegedly withheld information, if disclosed, would have a natural tendency to influence, or be capable of influencing, a government function."

- Merck, on the other hand, argues that plaintiffs must show "that the allegedly withheld information, if disclosed, in reasonable probability would have led to a different

> regulatory outcome such as refusal to approve Vioxx for marketing or requiring a label change."

Plaintiffs proposed definition is erroneous for several reasons. First, the definition would effectively make any relevant information sufficient to eliminate the presumption. Under the plaintiff's definition, virtually any information would qualify. Since the Texas Act was promulgated in an environment of tort reform, the legislature surely meant that the burden on plaintiffs be more than merely finding "some information" that "might" be capable of influencing the FDA. This Court may consider the circumstances surrounding a statute and the goals sought to be achieved by the legislature in construing a statute. *See Lexington Ins. Co. v. Strayhorn*, 209 S.W.3d 615 (Tex. 2005).

Second, the Texas Act requires that the withheld information be "causally related" to the plaintiff's injury. Unless withheld information would have resulted in some definite change by the FDA, either non-approval of the drug, or a labeling change, such with withheld information could not be causally related to a plaintiff's injury.

Thus, plaintiffs must prove by a preponderance of the evidence that required information was withheld from or misrepresented to the FDA, such that the allegedly withheld or misrepresented information, if disclosed or not misrepresented, would have led to a different regulatory outcome such as refusal to approve Vioxx for marketing or requiring a label change.

4. Relevant Information

The allegedly withheld or misrepresented information must relate to the same injury complained of by plaintiff.

C. Preemption of the Texas Act

The starting point of any preemption analysis concerning the Texas Act is *Buckman Co. v. Plaintiffs' Legal Committee,* 531 U.S. 341 (2001), where the Supreme Court held that state law "fraud on the FDA" claims are preempted by the Food, Drug and Cosmetic Act, 21 U.S.C. § 301, *et seq.* ("FDCA"). There, Buckman was a consulting company that assisted a manufacturer to obtain FDA approval for certain medical devices. Plaintiffs were consumers of these devices, who claimed personal injuries; plaintiffs sued Buckman alleging that Buckman made fraudulent representations to the FDA. Plaintiffs claimed that such misrepresentations were a "but for" cause of injuries: had the representations not been made, the FDA would not have approved the device, and plaintiffs would not have been injured. The Supreme Court held that such claims are preempted by the FDCA. The Court reasoned that it is the FDA's exclusive responsibility to "police fraud consistently with the Administration's judgment and objectives." *Id.* at 350. The Court observed that the FDA is empowered to investigate fraud and that citizens may report wrongdoing and petition the agency to take action. *Id.* at 349. Moreover, "fraud-on-the FDA claims would also cause applicants to fear that their disclosures to the FDA, although deemed appropriate by the Administration, will later be judged insufficient

in state court" resulting in a "deluge" of needless information on the FDA, potentially burdening the agency and delaying release of new products. *Id.* at 351.

Since *Buckman,* several courts have considered statutes similar to the Texas Act. In *Garcia v. Wyeth Ayerst Laboratories*, 385 F.3d 961 (6th Cir. 2004), the Sixth Circuit considered a Michigan law that immunizes a drug manufacturer from products liability suits if the drug was approved by the FDA unless the manufacturer intentionally withheld or misrepresented required information.[1] The court held the Michigan law was preempted to the extent that it permitted a state court to determine whether a drug

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[1] The statute provides, in relevant part: "(5) In a product liability action against a manufacturer or a seller, a product that is a drug is not defective or unreasonably dangerous, and the manufacturer or seller is not liable, if the drug was approved for safety and efficacy by the United States food and drug administration, and the drug and its labeling were in compliance with the United States food and drug administration's approval at the time the drug left the control of the manufacturer or seller. . . . This subsection does not apply if the defendant at any time before the event that allegedly caused the injury does any of the following:

(a) Intentionally withholds from or misrepresents to the United States food and drug administration information concerning the drug that is required to be submitted under the federal food, drug, and cosmetic act . . . , and the drug would have not been approved, or the United States food and drug administration would have withdrawn approval for the drug if the information were accurately submitted.

MICH. COMP. LAWS § 600.2946(5).

manufacturer committed fraud on the FDA. *Id.* at 966. However, such "inter-branch-meddling concerns that animated *Buckman*" do not arise when the "FDA *itself* determines that a fraud has been committed on the agency during the regulatory-approval process." *Id.* (emphasis in original) Thus, the court held that a plaintiff could only invoke the "fraud on the FDA" exception to the Michigan statute if the FDA itself determines that it was defrauded. Other courts have reached similar conclusions. *See, e.g., Henderson v. Merck & Co.*, 2005 WL 2600220 (E.D. Pa., Oct. 11, 2005); *Kobar v. Novartis Corp.*, 378 F. Supp. 2d 1166, 1172-74 (D. Ariz. 2005).

Plaintiffs, however, rely on *Desiano v. Warner-Lambert & Co.*, 467 F.3d 85 (2d Cir. 2006), which reached a different conclusion and suggested three reasons why the *Garcia* analysis is flawed. First, plaintiffs correctly note that there is a presumption against preemption. While such a presumption exists, *see Cipollone v. Liggett Group, Inc.*, 505 U.S. 504, 518 (1992), the Supreme Court in *Buckman* expressly held that no such presumption against preemption existed in that case. "The relationship between a federal agency and the entity it regulates is inherently federal in character because the relationship originates from, is governed by, and terminates according to federal law." 531 U.S. at 347. Because, in that case, the medical device manufacturer's dealings with the FDA were prompted by federal law, "no presumption against preemption obtains in this case." *Id.* The same analysis must apply with no less force to drug manufacturers. Indeed, the State of Texas, by enacting the Texas Act, has placed the relationship between drug manufacturer and FDA in issue.

Second, plaintiffs argue that *Buckman* is inapplicable since it involved a non-traditional suit based entirely on a fraud on the FDA theory, whereas these suits allege traditional products liability theories. This is a distinction without a difference. Under the Texas Act, in order to pursue a failure to warn case, plaintiffs must prove that required and material information was withheld from the FDA. Whether it is an element of plaintiffs' cause of action, or a way to defeat an affirmative defense, the proof is the same. All of the federalism concerns expressed in *Buckman* still apply. The requisite showing under the Texas Act is analogous to and sufficiently equivalent to plaintiffs' asserting a claim of fraud on the FDA that the claim is preempted under *Buckman*.

Finally, plaintiffs argue that the proof required under the Texas Act is different from a "fraud on the FDA" complaint. Plaintiffs argue that mere inadvertent withholding of information is sufficient to puncture the rebuttable presumption of the Texas Act[2], whereas intentional fraud was at issue in *Buckman*, and, indeed, part of the statute in Michigan. This Court is not persuaded by this argument. The logic of *Buckman* was that the FDA promulgates detailed data submission requirements and is fully empowered to investigate wrongful withholding by manufacturers.

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[2] The Court notes that the Texas Act uses the word "misrepresents" which could imply an element of intent, depending on whether the misrepresentation required is intentional or negligent. However, for purposes of this motion, the Court will assume no scienter is required since the statute disjunctively includes "withheld from" as sufficient to eliminate the statutory rebuttable presumption.

531 U.S. at 1017. If anything, the argument that *Buckman* involved a claim with an element of scienter, whereas the Texas Act requires only inadvertent withholding undermines plaintiffs' argument. State courts traditionally adjudicate a party's state of mind, *e.g.*, whether fraud occurs. Indeed, a state court is probably better suited than a federal agency to determine whether an intentional misrepresentation occurred as opposed to an inadvertent omission. The key issue for purpose of presumption analysis is not whether information was intentionally withheld, but whether the federal regulation is so pervasive as to leave no room for state regulation. Given the extent of federal regulation, and the extent to which the FDA is empowered to investigate and regulate drug manufacturers who fail to provide required information, permitting a Texas jury or judge to make the same inquiry would impinge on a uniquely federal issue.

All of the concerns raised by the Supreme Court in *Buckman* would manifest themselves if the motion for summary judgment were denied. *Buckman* noted that manufacturers might "deluge" the FDA with information it neither needed nor wanted in order to defend state tort claims. 531 U.S. at 351. This could potentially impede the regulatory process. The *Buckman* concern of deluging the FDA could well come true if manufacturers were forced to make data submissions defensively in order to ensure that the presumption of the Texas Act remained in place.

There is no question but that the FDA has not made a determination that material and relevant

information was either withheld or misrepresented concerning Vioxx.

C. Severability

Plaintiffs argue that if subsection (b)(1) is preempted, then the entirety of section 82.007 must fall, leaving no presumption that Merck's is not liable with respect to the allegations involving failure to provide adequate warnings. This argument fails. First, plaintiffs can still avail themselves of (b)(1) if the FDA determines that required information was withheld. The issue is who makes the determination—the FDA or a Texas court or jury.

Second, the Texas Act is severable. Texas law currently provides that:

> (c) In a statute that does not contain a provision for severability or nonseverability, if any provision of the statute or its application to any person or circumstance is held invalid, the invalidity does not affect other provisions or applications of the statute that can be given effect without the invalid provision or application, and to this end the provisions of the statute are severable.

TEX. GOV'T CODE § 311.032(c). Unless the legislature provides for nonseverability, the Government Code provides that the statute is severable. Even if subsection (b)(1) is invalid, the remaining statute can be given effect.

Finally, in passing the Texas Act, the legislature expressly considered the possibility that the law would not survive a *Buckman* analysis.[3] Yet, notwithstanding this forewarning, the legislature did not insert a nonseverability provision into § 82.007.

D. Conclusion on Preemption

For the forgoing reasons, Merck's motion for partial summary judgment is granted and subsection (b)(1) of TEX. CIV. PRAC. & REM. CODE ANN. §82.007 is preempted to the extent that someone other than the FDA is being asked to make the determination. Plaintiffs cannot rely on subsection (b)(1) unless and until the FDA makes the required findings under (b)(1).

3. Merck's Alternative Motion

Merck argued alternatively that even if the Texas Act is not preempted, a no evidence motion for summary judgment should nevertheless be granted. Merck argues that plaintiffs do not have sufficient evidence to rebut the presumption.

In response, plaintiffs submit the affidavits of various experts. However, because of this Court's

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[3] For example, Baylor Law School Dean Bradley Tobin testified in Senate committee hearings that § 82.007 could very well be challenged on *Buckman* grounds. Hearings on Tex. H.B. 4 Before Senate State Affairs Comm., 78th Leg., R.S. at 23-24 (May 5, 2003).

ruling on preemption, it is not necessary to rule on Merck's alternative motion.

Plaintiff's motion to strike Merck's Summary Judgment evidence is Denied.

Plaintiff's claim of failure to warn is hereby severed from this Master Docket and will henceforth be under cause number 2005-59499A and in the original trial court as Cause No. 2005-58543A. The pleadings in this severed cause shall consist of plaintiff's petition(s), defendants' answer(s), Merck's motion for partial summary judgment and all responses, replies, rebuttals and other briefs and memoranda concerning the motion for summary judgment.

This is a final order and is appealable.

It is further ordered that any appeal from this Order be expedited pursuant to Tex. R. Jud. Admin. 13.9(c) as this order is made in MDL pretrial proceedings.

Signed April 19, 2007.

/s/

Hon. Randy Wilson

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No. 06-1249

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IN THE

Supreme Court of the United States

WYETH,

Petitioner,

v.

DIANE LEVINE,

Respondent.

On Writ of Certiorari to the Supreme Court of Vermont

BRIEF OF AMICI CURIAE VERMONT, ALABAMA, ALASKA, ARIZONA, ARKANSAS, CALIFORNIA, COLORADO, CONNECTICUT, DELAWARE, FLORIDA, GEORGIA, HAWAII, IDAHO, ILLINOIS, INDIANA, IOWA, KANSAS, KENTUCKY, LOUISIANA, MAINE, MARYLAND, MASSACHUSETTS, MINNESOTA, MISSISSIPPI, MISSOURI, MONTANA, NEVADA, NEW HAMPSHIRE, NEW JERSEY, NEW MEXICO, NEW YORK, NORTH CAROLINA, NORTH DAKOTA, OHIO, OKLAHOMA, OREGON, PENNSYLVANIA, RHODE ISLAND, SOUTH CAROLINA, SOUTH DAKOTA, TENNESSEE, UTAH, WEST VIRGINIA, VIRGINIA, WASHINGTON, WISCONSIN, AND WYOMING IN SUPPORT OF RESPONDENT

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Caleb Nelson, *Preemption*, 86 Va. L. Rev. 225 (2000) 17, 27

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Margaret J. Porter, *The* Lohr *Decision: FDA Perspective and Position*, 52 Food & Drug L.J. 7 (1997) 10, 32

Restatement (Third) of Torts: Prods. Liab. 8

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David C. Vladeck, *Preemption and Regulatory Failure*, 33 Pepp. L. Rev. 95 (2005) 8

INTEREST OF THE AMICI CURIAE

The forty-seven amici states, as separate sovereigns in our federal system, have two important interests in the outcome of this case. *First*, the amici are responsible for the enforcement of laws that safeguard public health, safety, and welfare. We therefore have a fundamental interest in preserving the appropriate balance of authority between the states and the federal government. Of significant concern to the amici states are cases involving the amorphous concept of implied preemption. In such cases, Congress has not expressly stated which state-law causes of action—if any—should be eliminated. In our view, courts should only rarely infer that Congress, although silent on the issue, nonetheless intended to displace state law where it is possible to comply with both state and federal law.

Second, this particular case is of crucial importance because the position espoused by Petitioner and the United States would represent an unprecedented elimination of remedies available to consumers injured by drugs. Common law duties play a pivotal role in protecting the health and welfare of the states' citizens. Through the evolution of state common law and by legislative enactments, the states have developed and refined their tort systems to accomplish that end. The amici therefore urge this Court to affirm the decision of the Vermont Supreme Court and reject the sweeping argument advanced by Petitioner and the United States.

INTRODUCTION AND SUMMARY OF ARGUMENT

This case involves the preemptive scope of the Federal Food, Drug, and Cosmetic Act of 1938 (FDCA), as amended, 21 U.S.C. §§ 301-397. In contrast to the Medical Device Amendments of 1976 (MDA), 21 U.S.C. § 360k, which expressly preempts "different" or "addition[al]" state requirements with respect to medical devices, the FDCA does not contain an express preemption provision. Petitioner's "implied preemption" argument boils down to the proposition that this Court should construe the FDCA as though it did. In particular, Petitioner argues that Respondent's state-law claim is preempted because it is "impossible" for Petitioner to comply with both state- and federal-law duties (Pet. Br. 29) and because application of state law would "frustrate the public-health objectives underlying the FDCA." Pet. Br. 46. Neither contention has merit.

1. Petitioner's "impossibility" argument cannot be squared with the 70-year history of state tort law operating concurrently with FDA regulation. Injured individuals have long brought state damages actions predicated on faulty drug labels and drug designs. And for the first 60 or so years following the FDCA's enactment, the FDA found it perfectly "possible" for the two regulatory regimes to coexist. Indeed, during that time, the FDA did not even contend that the state actions frustrated achievement of the FDCA's objectives. The FDA's newly-minted assertion, embraced by Petitioner, that state tort law and the FDCA's requirements directly conflict fails the test of history.

2.a. Petitioner's implied frustration preemption argument founders on basic principles of statutory construction and separation of powers. This Court has recognized that the question whether a federal statute displaces state law is an issue of congressional intent. And when frustration preemption is alleged, the key inquiry is whether Congress intended to displace state laws that frustrate full accomplishment of federal objectives.

As a general matter, the answer is that Congress *sometimes* will wish to remove every obstacle in the way of accomplishing federal objectives as quickly and completely as possible. But Congress often has competing objectives, and legislation is often the product of compromise. Congress might conclude, for example, that state tort actions should proceed in order to provide remedies for injured consumers—even if that "frustrates" to some degree the federal goal of uniformity. Similarly, Congress might retain state tort actions as a compromise for having less strict federal standards.

In the end, this paradigmatic policy decision is for Congress, not the courts, to make. Congress knows how to express its intent to displace state laws that it believes stand as obstacles to federal objectives. Literally hundreds of federal statutes contain express preemption provisions. When Congress chooses *not* to include such a provision, that decision should be respected. Adherence to the plain language of federal statutes requires no less. Just as this Court no longer finds private rights of action (except in rare cases), this Court should no longer find frustration preemption (except in rare cases).

That conclusion is buttressed by principles of federalism. Congress's authority under the Commerce

Clause gives it vast opportunities to preempt state law. If the political process is to serve as a genuine check on that power, states must be given notice when their authority is at risk. Implied frustration preemption undermines that check. It also amounts to a presumption *in favor* of preemption because the court is presuming that Congress intended to displace state law. Our federal system should not countenance such a disregard of the states' reserved powers.

For these reasons, courts should infer frustration preemption only when no reasonable policy ground supports the application of state law. When reasonable policy grounds can be asserted both for and against preempting state law, Congress's silence should be construed as a decision *not* to displace state law. And when Congress does not intend to preempt state law on frustration preemption grounds, federal agencies lack the authority to decree that state laws should be preempted on this basis.

b. The FDCA does not express the intent to displace state laws when compliance with state and federal law is possible. Congressional intent to preempt Respondent's state tort action should be found, therefore, only if no reasonable policy grounds support allowing it to proceed. In fact, however, numerous reasonable policy justifications exist: *e.g.*, providing compensation to injured persons, producing new information on the risks of drugs, fear that the FDA is poorly funded and staffed, and the concern that the agency is not nimble enough to respond to information about the dangers posed by products.

Moreover, Congress expressly preempted state law with respect to *other* products regulated by the

FDA; and Congress failed to adopt an express preemption provision in the FDCA even though it was well aware of the long history of state tort actions against drug manufacturers. On top of that, the saving clause in the 1962 Amendments to the FDCA evinced specific intent to limit implied preemption as much as possible. In the end, the FDCA is not one of those rare federal statutes as to which courts should infer congressional intent to displace state laws in the name of frustration preemption.

ARGUMENT

This Court's docket is replete with cases addressing the meaning of express preemption provisions. See, *e.g.*, *Riegel v. Medtronic*, 128 S. Ct. 999 (2008); *Rowe v. N.H. Motor Transport Ass'n*, 128 S. Ct. 989 (2008); *Altria Group, Inc. v. Good*, No. 07-562. The FDCA is striking for its absence of such a provision. In the 70 years since its enactment, Congress has had ample opportunity to preempt state laws applicable to prescription drugs and drug labeling, but has declined to do so. The core issue in this case is what meaning should be attributed to Congress's refusal to express any intent to displace state laws affecting FDA-approved prescription drugs.

Petitioner and its amici essentially argue that the FDCA operates identically to the MDA—that Congress implicitly intended to preempt all state requirements "different from, or in addition to" the federal regulatory regime governing prescription drugs. Their expansive approach to impossibility and obstacle preemption cannot be reconciled with the history of drug regulation or with basic principles of statutory construction, separation of powers, and federalism.

I. It Is Possible To Comply With Both State Common Law And Federal Labeling Regulations Under The FDCA.

Petitioner's impossibility argument is straightforward: the "verdict in this case . . . rested on a state-law duty to change th[e] labeling" of Phenergan (Pet. Br. 33), but "unilaterally alter[ing] the labeling . . . would have been in violation of federal law and subject to enforcement action by FDA." Pet. Br. 30. Respondent's brief fully rebuts the contentions that federal law required Petitioner to distribute Phenergan only with the FDA-approved labeling and that the FDA specifically considered and rejected a label change that would have prohibited or limited intravenous-push injections. Resp. Br. 32-36. Respondent also rebuts Petitioner's more general contention that FDA pre-market approval of a drug label, by itself, is incompatible with a state-law failure-to-warn claim. *Id.* at 36-43. Rather than repeat those arguments, we will limit our submission on this issue to the following point.

Petitioner and other drug manufacturers have had to comply with both federal drug labeling obligations and state common law for 70 years. Far from presenting "irreconcilable" obligations, common law tort suits like the one at issue here have always coexisted with federal labeling requirements. Petitioner's impossibility arguments should therefore be rejected.

To be sure, policy arguments can be made that it might be *unwise* to permit state tort actions challenging labels that were approved by the FDA when the drug was first released. But policy arguments can also be made that a complementary state-federal scheme reasonably balances safety and efficacy in

the pharmaceutical industry while at the same time providing compensation to victims of wrongful injuries. For many years, the FDA itself agreed with the latter arguments. Regardless of who has the better of that policy dispute, one thing this history proves is this: It is *possible* to regulate prescription drugs by having the FDA pre-approve them (and their labels) while also having state juries impose liability when prescription drug labels are found to have provided inadequate warning.

1. This Court has recognized that the states are "vested with the responsibility of protecting the health, safety, and welfare of [their] citizens," and have "great latitude" when carrying out that responsibility. *United Haulers Ass'n, Inc. v. Oneida-Herkimer Solid Waste Mgmt. Auth.*, 127 S. Ct. 1786, 1795 (2007). "[C]ommon-law damages claims" are "a critical component of the States' traditional ability to protect the health and safety of their citizens." *Cipollone v. Liggett Group, Inc.*, 505 U.S. 504, 544 (1992) (Blackmun, J., joined by Kennedy and Souter, J.J., concurring in part and dissenting in part).

Prior to the FDCA's enactment in 1938, a common-law claim for negligence for the manufacture and sale of medicines was widely recognized. See, *e.g.*, *Boyd v. Coca Cola Bottling Works*, 177 S.W. 80, 81 (Tenn. 1915) (holding that drug, food, and beverage manufacturers owe a duty to consumers and that a "tort is committed, a legal right invaded, by practices which prejudice another's health"); *Thomas v. Winchester*, 2 Seld. 397, 1852 WL 4748 (N.Y. 1852) (holding a drug manufacturer liable for a patient's injury). And in the seven decades following the FDCA's passage, the states' traditional common-law

tort systems have continued to compensate injured consumers for injuries caused by prescription drugs.[1]

State tort actions took the federal regulatory regime into account, but in the form of the regulatory compliance defense, which allows juries to consider compliance with federal statutes and regulations when determining a manufacturer's liability. Robert B. Leflar & Robert S. Adler, *The Preemption Pentad: Federal Preemption of Products Liability Claims after* Medtronic, 64 TENN. L. REV. 691, 715 (1997); *Restatement (Third) of Torts: Prods. Liab.* § 4 Reporters' Note, cmt. e (1998) (stating that the vast majority of states permit the defense).

If these state tort actions placed prescription drug manufacturers in an impossible bind—forcing them to take actions under state law that federal law prohibited—one would have expected the drug manufacturers to raise the preemption defense at every opportunity. Yet drug companies did not begin to assert preemption as a routine defense until after this Court's ruling in *Cipollone* in 1992. See David C. Vladeck, *Preemption and Regulatory Failure*, 33 PEPP. L. REV. 95, 106 (2005). And when they did

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[1] See, *e.g.*, *Incollingo v. Ewing*, 282 A.2d 206 (Pa. 1971); *Sterling Drug, Inc. v. Yarrow*, 408 F.2d 978 (8th Cir. 1969); *Tinnerholm v. Parke, Davis & Co.*, 285 F. Supp. 432 (S.D.N.Y. 1968); *Phillips v. Roux Labs.*, 145 N.Y.S.2d 449 (N.Y. App. Div. 1955); *Abbott Labs. v. Lapp*, 78 F.2d 170 (7th Cir. 1935); *Valmas Drug Co. v. Smoots*, 269 F. 356 (6th Cir. 1920). See also *Riegel*, 128 S. Ct. at 1017 n.11 (Ginsburg, J., dissenting) (listing 12 other state-law tort actions brought between 1968 and 1975 involving FDA-approved drugs).

assert preemption, the courts almost universally rejected the defense.[2]

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[2] Federal Courts of Appeals: *Abbot v. American Cyanimid Co.*, 844 F.2d 1108, 1112 (4th Cir.), *cert. denied*, 488 U.S. 908 (1988); *Osburn v. Anchor Labs.*, 825 F.2d 908, 911-13 (5th Cir. 1987), *cert. denied*, 485 U.S. 1009 (1988); *Tobin v. Astra Pharm. Prods., Inc.*, 993 F.2d 528, 537 (6th Cir.), *cert. denied*, 510 U.S. 914 (1993); *Hill v. Searle Labs.*, 884 F.2d 1064, 1068 (8th Cir. 1989); *Wells v. Ortho Pharm. Corp.*, 788 F.2d 741, 746 (11th Cir.), *cert. denied*, 479 U.S. 950 (1986).

Federal District Courts: *In re Vioxx Prods. Liability Litig.*, 501 F. Supp. 2d 776, 788-789 (E.D. La. 2007); *In re Zyprexa Prods. Liability Litig.*, 489 F. Supp. 2d 230, 275-78 (E.D.N.Y. 2007); *Jackson v. Pfizer, Inc.*, 432 F. Supp. 2d 964, 966-68 (D. Neb. 2006); *Laisure-Radke v. Par Pharm., Inc.*, 426 F. Supp. 2d 1163, 1169 (W.D. Wash. 2006); *Weiss v. Fujisawa Pharm. Co.*, 464 F. Supp. 2d 666, 676 (E.D. Ky. 2006); *Perry v. Novartis Pharm. Corp.*, 456 F. Supp. 2d 678, 685-88 (E.D. Pa. 2006); *Witczak v. Pfizer, Inc.*, 377 F. Supp. 2d 726, 731-72 (D. Minn. 2005); *Cartwright v. Pfizer, Inc.*, 369 F. Supp. 2d 876, 882-87 (E.D. Tex. 2005); *Caraker v. Sandoz Pharm. Corp.*, 172 F. Supp. 2d 1018, 1029-44 (S.D. Ill. 2001); *Motus v. Pfizer, Inc.*, 127 F. Supp. 2d 1085, 1091-1100 (C.D. Cal. 2000); *Mazur v. Merck & Co.*, 742 F. Supp. 239, 245-48 (E.D. Pa. 1990); *In re Tetracycline Cases*, 747 F. Supp. 543, 546-50 (W.D. Mo. 1989); *Kociemba v. G.D. Searle & Co.*, 680 F. Supp. 1293, 1298-1300 (D. Minn. 1988); *Patten v. Lederle Labs.*, 655 F. Supp. 745, 747-50 (D. Utah 1987); *Knudsen v. Connaught Labs.*, 691 F. Supp. 1346, 1347 (M.D. Fla. 1987); *Wack v. Lederle Labs.*, 666 F. Supp. 123, 126-28 (N.D. Ohio 1987); *Foyle v. Lederle Labs.*, 674 F. Supp. 530, 532-34 (E.D.N.C. 1987); *Graham v. Wyeth Labs.*, 666 F. Supp. 1483, 1488-93 (D. Kan. 1987); *Stephens v. G.D. Searle*, 602 F. Supp. 379, 382 (E.D. Mich. 1985).

State Courts: *Carlin v. Superior Court*, 920 P.2d 1347, 1352-53 (Cal. 1996); *Wagner v. Roche Labs.*, 671 N.E.2d 252, 258 (Ohio 1996); *Washington State Physicians Ins. Exchange & Assocs. v. Fisons Corp.*, 858 P.2d 1054, 1068-70 (Wash. 1993); *Feldman v. Lederle Labs.*, 592 A.2d 1176, 1185-97 (N.J. 1991), *cert. denied*, 505 U.S. 1219 (1992).

2. If state tort actions placed prescription drug manufacturers in an impossible bind, one would also have expected the federal regulator to step in and try to cure that problem. To the contrary, however, the FDA's longstanding view—modified only this decade—was that drug manufacturers *can* comply with both the FDCA and state tort law.

For example, in 1979 and 1998, the FDA maintained in preambles to drug regulations that state tort law did not interfere with federal regulation. *Prescription Drug Product Labeling; Medication Guide Requirements*, 63 Fed. Reg. 66378, 66384 (Dec. 1, 1998) ("FDA does not believe that the evolution of state tort law will cause the development of standards that would be at odds with the agency's regulations."); *id.* (FDA "regulations establish the minimum standards necessary, but were not intended to preclude the states from imposing additional labeling requirements."); *Labeling and Prescription Drug Advertising; Content and Format for Labeling for Human Prescription Drugs*, 44 Fed. Reg. 37434, 37437 (June 26, 1979) ("It is not the intent of the FDA to influence the civil tort liability of the manufacturer.").

And as recently as 1997, then-FDA Chief Counsel Margaret Porter opined that Congress "did not intend to preempt state tort remedies for injury to individual consumers." Margaret J. Porter, *The* Lohr *Decision: FDA Perspective and Position*, 52 FOOD & DRUG L.J. 7, 9 (1997). The "FDA's view is that FDA product approval and state tort liability usually operate independently, each providing a significant, yet distinct, layer of consumer protection." *Id.* at 11.

The *content* of the FDCA and its pre-approval process did not change between 1979 and 2002, when

the FDA first announced its new pro-preemption position. The "possible" did not suddenly become "impossible." Drug manufacturers were not suddenly barred from revising their labels to deal more effectively with safety concerns; nor did they suddenly become incapable of paying compensation to injured consumers based on pre-approved labels. Rather, what changed was Executive Branch policy concerning the efficacy of allowing state tort actions to proceed against drug companies. Impossibility preemption requires far more than that.

II. The FDCA Does Not Impliedly Preempt State Tort Actions That Purportedly "Frustrate" The Statute's Objectives.

The history described in § I not only undermines Petitioner's contention that compliance with state tort law and the FDCA is impossible; it also undermines Petitioner's separate contention that state tort law "stands as an obstacle to the accomplishment and execution of the full purposes and objectives of Congress" in enacting the FDCA. Pet. Br. 40 (quoting *Hines v. Davidowitz*, 312 U.S. 52, 67 (1941)).

Petitioner's reliance on obstacle, or frustration, preemption fails for an additional reason: the FDCA expresses no intent whatsoever to preempt any and all state laws that might frustrate "the accomplishment and execution of the full purposes and objectives of Congress." When Congress passes a detailed statute expressing its specific intent on myriad matters, but does not address the displacement of state law, the judicial role is to give effect to the congressional language—including Congress's silence.

Lost in Petitioner's argument is any reference to principles of statutory construction and the infe-

rences that ought to be drawn by comparing the MDA, which contains an express preemption provision, with the FDCA, which does not. The policy-laden decision whether to displace state laws that might stand in tension with federal objectives is for Congress to make. In hundreds of statutes, Congress expressed its intent to preempt state laws that it felt would frustrate the achievement of federal objectives. Congress chose not to include such a provision in the FDCA, a decision that this Court should respect.

A. Principles of statutory construction, separation of powers, and federalism dictate that courts should only rarely displace state law under the doctrine of implied frustration preemption.

Just as this Court no longer reads implied rights of action into statutes except in rare circumstances —regardless of whether such a right of action would further a statute's objectives—so too should this Court no longer find implied frustration preemption except in rare circumstances. In both instances, the decision whether to effectuate Congress's objectives through that particular means is a policy-laden decision that Congress, not the courts, should make.

And in both instances, Congress has shown that it knows how to express its intent. The proper judicial role—particularly given the federalism implications of displacing state law—is to respect the statutory text and Congress's failure to express preemptive intent. So long as Congress would have had reasonable policy grounds *not* to displace state law, courts should not infer frustration preemption.

1. Whether a federal statute preempts state law under the doctrine of implied frustration preemption depends on congressional intent to displace state law.

The Supremacy Clause is the constitutional choice-of-law provision which declares that federal law trumps state law when the two are in direct conflict. But the Clause itself resolves few, if any, preemption disputes. Rather, as the Court has stated time and again, the question in preemption cases "is basically one of congressional intent. Did Congress, in enacting the Federal Statute, intend to exercise its constitutionally delegated authority to set aside the laws of a State?" *Barnett Bank of Marion County, N.A. v. Nelson*, 517 U.S. 25, 30 (1996).

That general statement masks critical nuances, because the precise target of the statutory inquiry varies greatly depending on the type of preemption at issue. In particular, the inquiry differs depending on whether preemption allegedly arises from (1) a statutory provision that expressly preempts state laws, (2) a direct conflict between federal and state law such that it would be impossible to comply with both, or (3) the claim that operation of state law would frustrate achievement of the federal statute's objectives. As will be shown below, when a party claims that a federal statute preempts state law based on implied frustration preemption, the key statutory construction inquiry is whether Congress—notwithstanding its silence on the issue—still in-

tended to displace state laws that frustrate certain purposes or objectives of the federal act.[3]

Express preemption. When preemption is asserted based on an express preemption provision, the statutory construction inquiry concerns the meaning and scope of the provision. To be sure, this inquiry can be complicated by the presence of a saving clause that preserves certain types of state laws from the force of the preemption provision. See, *e.g.*, *Geier v. American Honda Motor Co.*, 529 U.S. 861, 867-74 (2000). But, critically for present purposes, the inquiry in an express preemption case is *not* whether Congress intended to displace state law in the first place. The express preemption provision, by definition, has answered that question.

Impossibility Preemption. Preemption also occurs when "compliance with both federal and state regulations is a physical impossibility." *Florida Lime & Avocado Growers, Inc. v. Paul*, 373 U.S. 132, 142-43 (1963). The paradigmatic case of "impossibility preemption" occurs when a federal statute says "private entities must do X" and a state law says "private entities may not do X." In that situation, the state law is displaced by direct operation of the Supremacy Clause, which gives the federal statute precedence over a state law that would nullify its operation. The statutory construction inquiry concerns the substantive meaning of the federal statute: what is the meaning of X? The inquiry, again, is *not*

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[3] We do not separately address "field preemption" because the difference between field and non-field preemption is the scope of preempted state law, not the manner by which it is preempted. See 1 Laurence H. Tribe, *American Constitutional Law* 1177 (3d ed. 2000) (noting that field preemption "may fall into any of the . . . categories" of preemption).

whether Congress intended to displace certain state laws.

For example, to borrow from Professor Hart's famous example,[4] if a federal statute declares that "no vehicles shall be permitted in public parks," and a state law provides that "bicycle riding is permitted in parks," the sole statutory construction inquiry would be the meaning of the substantive term "vehicles." If "vehicles" includes bicycles, the state law is preempted by operation of the Supremacy Clause—without any need for Congress to have specifically stated "we intend to displace state laws that directly contradict this statute."

Implied Frustration Preemption. Even where there is no express preemption and it is possible to comply with both federal and state law, this Court has also asked whether the state law nonetheless should be preempted because it would frustrate the full achievement of the federal objectives. See *Hines*, 312 U.S. at 67. In answering that question, the statutory construction inquiry has two distinct targets.

The first inquiry is the same one undertaken in impossibility-preemption cases: discerning the substantive meaning of the federal statute. But in contrast to impossibility-preemption cases, that inquiry does not end the matter. Even if we know exactly what federal standards and rules Congress intended to adopt, there remains the separate question whether Congress intended to displace state laws to better effectuate those standards and rules and the purposes underlying them.

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[4] See H.L.A. Hart, *Positivism and the Separation of Law and Morals*, 71 HARV. L. REV. 593, 607 (1958).

The Supremacy Clause tells us that *if* Congress intended to displace state laws when they frustrate the achievement of certain federal objectives, that federal command controls. The Clause does not, however, answer the predicate question whether Congress so intended. That issue is a matter of statutory construction.

Critically, it is simply not the case that Congress always, or even usually, intends to preempt any and all state laws that might somehow "frustrate" achievement of one of its objectives. For example, one goal of Congress might be to "foster[] uniformity in . . . regulations," but that objective may not be "unyielding." *Sprietsma v. Mercury Marine*, 537 U.S. 51, 70 (2002). A state tort action that frustrates the goal of uniformity might advance legislators' expectation that injured consumers have access to remedies. *Id.* at 64 (state tort actions, "unlike most administrative and legislative regulations[,] necessarily perform an important remedial role in compensating accident victims").

Similarly, Congress might conclude that state tort liability provides a necessary supplement to a regulatory regime by "spurring change in regulatory or corporate procedures, as well as extending knowledge about drug risks by adding to the evidence available for evaluation by physicians, patients, and regulators." Aaron Kesselheim & Jerry Avorn, *The Role of Litigation in Defining Drug Risks*, 297 JAMA 308, 310 (2007); see also *Bates v. Dow Agrosciences LLC*, 544 U.S. 431, 451 (2005) ("tort suits can serve as a catalyst" to improve industry and federal regulatory practices).

Or a statute might reflect a compromise in which legislators who wanted stricter federal standards

settled for laxer standards in exchange for *not* displacing state tort actions. See *Landgraf v. USI Film Prods.*, 511 U.S. 244, 286 (1994) ("Statutes are seldom crafted to pursue a single goal, and compromises necessary to their enactment may require adopting means other than those that would most effectively pursue the main goal.").

As Professor Nelson has explained, even if we "suppose that all members of Congress can agree on the 'full purposes and objectives' behind a particular federal statute[,] [t]here still is no reason to assume that they would want to displace whatever state law makes achieving those purposes more difficult." Caleb Nelson, *Preemption*, 86 VA. L. REV. 225, 280 (2000). For as this Court "has acknowledged outside the realm of preemption, 'no legislation pursues its purposes at all costs,' and 'it frustrates rather than effectuates legislative intent simplistically to assume that whatever furthers the statute's primary objective must be the law.'" *Id.* (quoting *Rodriguez v. United States*, 480 U.S. 522, 525-26 (1987)).

Amici Chamber of Commerce and Product Liability Advisory Council (PLAC) are therefore wrong when they assert that congressional intent to displace state law is irrelevant to the implied frustration preemption inquiry. See Chamber Br. 23-26; PLAC Br. 16 ("Conflict preemption does not depend on an inference of congressional intent."). That is true only when compliance with both state and federal law is impossible. At that point, the Supremacy Clause kicks in and nullifies state law. Short of impossibility, the displacement of state law is not *necessary*; rather, it is a policy judgment. And Congress, not the courts, is the appropriate institution to make that policy judgment.

The Chamber acknowledges that the issue "is a matter of judgment" that requires courts to discern congressional "purpose" and whether the tension between state law and that purpose "is sufficient." Chamber Br. 24, 25. But, argues the Chamber, "[t]he law is filled with broad concepts— reasonableness, probable cause, excusable neglect, good cause, ordinary care—that call for the judicial exercise of judgment." *Id.* at 25. That is no doubt true, but the courts' role in interpreting statutes is far different from their role adjudicating tort and contract actions. When construing a statute, a court's "role is to interpret the language of the statute enacted by Congress," not to "satisfy policy preferences of the" parties, which "are battles that should be fought among the political branches and the industry." *Barnhart v. Sigmon Coal Co.*, 534 U.S. 438, 461-62 (2002).

In short, sometimes Congress will decide as a policy matter that achievement of certain statutory ends warrants casting aside all state laws that might hinder attainment of those ends. Sometimes, however, Congress will decide as a policy matter (or as a compromise) that competing interests served by state law—for example, providing remedies to injured persons—outweigh the costs imposed on a particular federal objective. When assessing whether a federal statute preempts a state law based on implied frustration preemption, a court must decide how Congress resolved that policy question.

As we explain below, ordinary tools of statutory construction dictate that when Congress has not spoken to the issue of preemption, courts should only rarely conclude that Congress nonetheless intended

to displace state laws that purportedly frustrate achievement of one of the federal statutory goals.[5]

2. Standard tools of statutory construction militate against finding implied frustration preemption.

a. Statutory interpretation begins, of course, with the text. "When the statutory language is plain, the sole function of the courts—at least where the disposition required by the text is not absurd—is to enforce it according to its terms." *Arlington Cent. School Dist. Bd. of Educ. v. Murphy*, 548 U.S. 291, 296 (2006) (internal quotation marks omitted). The terms of statutes—such as the FDCA—that do not contain a preemption provision are clear: they express no apparent intent to displace state law.

When Congress wishes to displace state law in order to achieve federal objectives more efficiently, it knows how to do so. By one count, Congress has enacted 355 statutes that contain express preemption provisions. See James T. O'Reilly, *Federal Preemption of State & Local Law* § 1.2, at 2 (2006). Congress's decision *not* to express any intent to displace state law should therefore be given great weight.

Indeed, this Court routinely defers to congressional silence where Congress has expressly spoken on a given issue in other statutes. See, *e.g.*, *Kimbrough v. United States*, 128 S. Ct. 558, 571 (2007) ("Drawing

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[5] We recognize that the Court stated in *Geier* that it did not wish to "drive[] a legal wedge" between impossibility and implied frustration preemption. 529 U.S. at 873. But *Geier* cannot reasonably be construed as suggesting that there are no differences whatsoever between how the two types of preemption are analyzed.

meaning from silence is particularly inappropriate here, for Congress has shown that it knows how to direct sentencing practices in express terms."); *Whitfield v. United States*, 543 U.S. 209, 216-217 (2005) ("Congress has included an express overt-act requirement in at least 22 other current conspiracy statutes, clearly demonstrating that it knows how to impose such a requirement when it wishes to do so. . . . Where Congress has chosen *not* to do so, we will not override that choice. . . ."); *Dole Food Co. v. Patrickson*, 538 U.S. 468, 476 (2003) ("Where Congress intends to refer to ownership in other than the formal sense, it knows how to do so. Various federal statutes refer to 'direct and indirect ownership.' The absence of this language in 28 U.S.C. § 1603(b) instructs us that Congress did not intend to disregard structural ownership rules." (internal citations omitted)); *Gwaltney of Smithfield, Ltd. v. Chesapeake Bay Found., Inc.*, 484 U.S. 49, 57 (1987) ("Congress has demonstrated in . . . other statutory provisions that it knows how to avoid this prospective implication by using language that explicitly targets wholly past violations."); see also *Watters v. Wachovia Bank, N.A.*, 127 S. Ct. 1559, 1582 (2007) (Stevens, J., dissenting) ("To begin with, Congress knows how to authorize executive agencies to preempt state laws. It has not done so here." (internal footnote omitted)).

When the Court declines to read unexpressed preemptive intent into federal statutes, it acts in a manner consistent with well-established statutory canons. One "cardinal principle of statutory construction" is that "a statute ought . . . to be so construed that, if it can be prevented, no clause, sentence, or word shall be superfluous, void, or insignificant." *Duncan v. Walker*, 533 U.S. 167, 174 (2001) (internal quotation marks omitted). Although the

anti-surplusage canon is typically employed to understand the meaning of one congressional enactment, its logic applies to construing separate statutes. Inferring frustration preemption makes surplusage out of many of Congress's express preemption provisions. An obvious example is the MDA's preemption provision, which serves no purpose if Petitioner's frustration preemption theory is correct.

Second, "where Congress includes particular language in one section of a statute but omits it in another section of the same Act, it is generally presumed that Congress acts intentionally and purposefully in the disparate inclusion or exclusion." *Russello v. United States*, 464 U.S. 16, 23 (1983) (internal quotation marks and citations omitted). Although, as with the anti-surplusage canon, this principle speaks to the "inclusion or exclusion" within a statute, its logic also applies when comparing statutes. When Congress includes preemption provisions in more than 350 statutes and does not include such provisions in other statutes, Congress should be "presumed" to have "act[ed] intentionally and purposefully."

A further reason not to infer congressional intent to displace state laws in the face of congressional silence is the difficulty of discerning Congress's purposes. Frustration preemption is premised on state laws being an "obstacle to the accomplishment and execution of the full purposes and objectives of Congress." *Hines*, 312 U.S. at 67. What if, however, the federal statute was the product of a compromise or contains multiple "purposes and objectives" that are in some tension with each other? See *Fitzgerald v. Racing Ass'n of Cent. Iowa*, 539 U.S. 103, 108 (2003) (noting that the state law under review, "like most

laws, might predominantly serve one general objective . . . while containing subsidiary provisions that seek to achieve other desirable (perhaps even contrary) ends as well, thereby producing a law that balances objectives but still serves the general objective when seen as a whole"). A state law might frustrate accomplishment of the "general objective," but further "achieve[ment]" of "other desirable . . . ends." *Id.* Only the statutory text can resolve whether Congress intended to preempt state law in such circumstances.

Given these considerations, it is not surprising that a majority of the members of the Court has expressed concern with the concept of implied frustration preemption. See *Bates*, 544 U.S. at 459 (Thomas, J., joined by Scalia, J., concurring in the judgment in part and dissenting in part) (approving "th[e] Court's increasing reluctance to expand federal statutes beyond their terms through doctrines of implied pre-emption"); *Geier*, 529 U.S. at 907 (Stevens, J., joined by Souter, Thomas, and Ginsburg, JJ., dissenting) (discussing the importance of "prevent[ing] federal judges from running amok with our potentially boundless (and perhaps inadequately considered) doctrine of implied conflict pre-emption based on frustration of purposes"); *Gade v. National Solid Wastes Mgmt. Ass'n*, 505 U.S. 88, 111 (1992) (Kennedy, J., concurring in part, concurring in judgment) ("A freewheeling judicial inquiry into whether a state statute is in tension with federal objectives would undercut the principle that it is Congress rather than the courts that pre-empts state law.").

b. This approach to implied frustration preemption—focusing on text, not on furthering perceived congressional purpose—parallels the Court's ap-

proach to implied rights of action. Before 1975, the Court "placed considerable emphasis upon the desirability of implying private rights of action in order to provide remedies thought to effectuate the purposes of a given statute." *Transamerica Mortgage Advisors, Inc. v. Lewis*, 444 U.S. 11, 15 (1979). As a result, the Court's "probe of the congressional mind . . . never focused squarely on private rights of action, as distinct from the substantive objects of the legislation." *Virginia Bankshares, Inc. v. Sandberg*, 501 U.S. 1083, 1103 (1991). This changed in a series of cases beginning with *Cort v. Ash*, 422 U.S. 66 (1975).

The key inquiry now is whether Congress specifically intended to create a private right of action. See *Virginia Bankshares*, 501 U.S. at 1104; *Merrell Dow Pharm. Inc. v. Thompson*, 478 U.S. 804, 812 n.9 (1986) (collecting cases). And "unless this congressional intent can be inferred from the language of the statute, the statutory structure, or some other source, the essential predicate for implication of a private remedy simply does not exist." *Northwest Airlines, Inc. v. Transport Workers*, 451 U.S. 77, 94 (1981). Although not dispositive, "congressional silence . . . is thus a serious obstacle" to finding private rights of action. *Virginia Bankshares*, 501 U.S. at 1104.

The Court changed its approach to implying private rights of action for many reasons, one of which has particular resonance here. The Court observed in *Virginia Bankshares* that, while the text and legislative history of § 14(a) of the Securities Exchange Act of 1934, 15 U.S.C. § 78n(a), "carry the clear message that Congress meant to protect investors from misinformation . . ., it is just as true that Congress was reticent with indications of how far this protec-

tion might depend on self-help by private action." 501 U.S. at 1103-04. Congress does not pursue its objectives at all costs and through all means. It is therefore up to Congress, not the courts, to specify the means—whether they be private rights of action or the displacement of state law.

3. Principles of federalism further militate against finding implied frustration preemption.

a. This Court has frequently recounted the reasons why the Framers adopted a federal structure of government and the advantages that accrue from it. Allowing States to exercise continued power ensures that government is "more sensitive to the diverse needs of a heterogeneous society"; "increases opportunity for citizen involvement in democratic processes"; "allows for more innovation and experimentation in government"; and "makes government more responsive by putting the States in competition for a mobile citizenry." *Gregory v. Ashcroft*, 501 U.S. 452, 458 (1991).

When state laws are preempted, none of those interests is served. This concern may not have been paramount earlier in the Republic, when Congress's powers were viewed as narrower, and federal law was "generally interstitial in its nature." Henry M. Hart, Jr. and Herbert Wechsler, *The Federal Courts and the Federal System* 470 (2d ed. 1973). Now, however, Congress's authority under the Commerce Clause is vast, see *Gonzales v. Raich*, 545 U.S. 1, 17 (2005) (confirming Congress's "power to regulate purely local activities" that substantially affect interstate commerce), and the opportunities to preempt state law are correspondingly broad.

Recognizing this concern, the Court has adopted a series of clear statement rules applicable when Congress encroaches upon state powers. See, *e.g.*, *Gregory*, 501 U.S. at 460-61 (adopting "plain statement" rule when Congress "would upset the usual constitutional balance of federal and state powers"); *Atascadero State Hosp. v. Scanlon*, 473 U.S. 234, 242 (1985) (requiring plain statement before construing statute to abrogate states' sovereign immunity); *Rice v. Santa Fe Elevator Corp.*, 331 U.S. 218, 230 (1947) (stating "assumption that the historic police powers of the States were not to be superseded by the Federal Act unless that was the clear and manifest purpose of Congress").

These rules serve a crucial structural function: "inasmuch as th[e] Court in *Garcia* [*v. San Antonio Metropolitan Transit Authority*, 469 U.S. 528 (1985)] has left primarily to the political process the protection of the States against intrusive exercises of Congress' Commerce Clause powers, we must be absolutely certain that Congress intended such an exercise." *Gregory*, 501 U.S. at 464. States cannot protect their interests through the political process if Congress has not signaled that it intends to trench on the states' domain.

The doctrine of broad implied frustration preemption is irreconcilable with these principles. Indeed, the doctrine amounts to a presumption *in favor* of preemption because the court is presuming that Congress, although silent on the issue, would have wanted state law displaced. This not only conflicts with basic canons of statutory construction and the judiciary's institutional role, see §§ II(A)(1) and (2), *supra*, but undermines the protections the political process is designed to afford the states. As then-

Justice Stone once wrote, "[a]t a time when the exercise of the federal power is being rapidly expanded through Congressional action, it is difficult to overstate the importance of safeguarding against such diminution of state power by vague inferences as to what Congress might have intended if it had considered the matter or by reference to our own conceptions of a policy which Congress has not expressed and which is not plainly to be inferred from the legislation which it has enacted." *Hines*, 312 U.S. at 75 (Stone, J., dissenting).

b. As noted above, the longstanding presumption against preemption is one tool for protecting the states' status as "independent sovereigns in our federal system." *Medtronic, Inc. v. Lohr*, 518 U.S. 470, 485 (1996) quoted in *Bates*, 544 U.S. at 449. "This assumption provides assurances that the federal-state balance will not be disturbed unintentionally by Congress or unnecessarily by the courts." *Jones v. Rath Packing Co.*, 430 U.S. 519, 525 (1977) (internal quotation and citation omitted).

The arguments set forth in §§ II(A)(1) and (2), *supra*, are independent from, but complementary to, the presumption against preemption. Principles of statutory construction and the proper institutional roles of Congress and the courts dictate that implied frustration preemption should only rarely be found; federalism principles reinforce that conclusion. The federalism-based presumption against preemption, and its concomitant clear-statement rule, leads to the same result.

The Chamber and PLAC devote most of their energies to arguing that the presumption against preemption does not apply to cases involving implied preemption. Their argument fails on its own terms,

as others have explained.[6] But more fundamentally, that argument is beside the point because it fails to reckon with the statutory construction, separation of powers, and federalism concerns addressed herein. At the very least, in the implied frustration preemption context, the presumption against preemption is a tool for effectuating the conclusion that implied frustration preemption should rarely be found.[7]

4. Inferring frustration preemption is only proper when no reasonable policy ground supports applying state law.

We are not suggesting that frustration preemption can *never* be found. A state law might so undermine the achievement of manifest federal objectives that no reasonable legislator would have voted for a bill knowing that such a state law would operate. Conversely, however, a state law should not be displaced where a reasonable policy ground supports its application.

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[6] See generally Brief of Public Justice, P.C., as *Amicus Curiae*, *Warner-Lambert Co. v. Kent*, No. 06-1498, at 5-29 (demonstrating that this Court has long and often applied the presumption in implied-preemption cases and explaining the purposes of the presumption in such cases).

[7] The Chamber (Br. 14, 18) and PLAC (Br. 14-15, 17) both rely heavily on Professor Nelson's conclusion that the presumption against preemption lacks a historical basis, but they fail to mention his conclusions that "the modern doctrine of 'obstacle' preemption has no place as a doctrine of constitutional law," that "obstacle preemption cannot be defended as a general doctrine of statutory interpretation," and that the presumption against preemption "makes some sense within the framework that the Supreme Court has developed for preemption cases" by "offset[ting] its . . . expansive formulations of 'implied' preemption." 86 VA. L. REV. at 266, 290, 304.

This "reasonable policy ground" rule implements the statutory construction, separation-of-powers, and federalism concerns discussed above. The choice whether to preempt state law is for Congress to make. It knows how to express its intent to displace state laws when that is its intent; and the interests served by our federal system are undermined when state laws are implicitly preempted by federal acts. Taken together, the general rule must be that courts should not "expand federal statutes beyond their terms through doctrines of implied pre-emption." *Bates*, 544 U.S. at 459 (Thomas, J., concurring in the judgment in part and dissenting in part).

Congress, not the courts, is charged with "the difficult policy choice[]" whether to displace state laws that stand in tension with certain federal objectives. *Ewing v. California*, 538 U.S. 11, 28 (2003). If reasonable policy arguments can be asserted both for and against displacement of state law, congressional silence is properly construed as a decision *not* to displace state law.

5. Federal agencies lack the authority to deem state laws preempted under the doctrine of implied frustration preemption.

When the ordinary tools of statutory construction reveal that Congress did not intend to displace state law, that ought to end the implied frustration preemption inquiry. As occurred here, however, federal agencies sometimes independently assert their view that state laws that frustrate achievement of federal objectives are preempted. See 71 Fed. Reg. 3922, 3934-35 (2006). The amicus brief by Professor Merrill on behalf of the Center for State Enforcement of Antitrust and Consumer Protection Laws compre-

hensively addresses the deference, if any, an agency should receive when it opines that state law is preempted. For present purposes, an additional observation is in order.

In *Alexander v. Sandoval*, 532 U.S. 275, 291 (2001), this Court held that "it is most certainly incorrect to say that language in a regulation can conjure up a private cause of action that has not been authorized by Congress. Agencies may play the sorcerer's apprentice but not the sorcerer himself." That holding fully applies to agency efforts to "conjure up" implied frustration preemption. It is one thing for an agency to exercise statutorily-delegated authority by promulgating a substantive regulation, and for that substantive regulation to preempt state laws that directly contradict it. See *Fidelity Fed. Sav. & Loan Ass'n v. De la Cuesta*, 458 U.S. 141 (1982) (agency rule permitting federal savings and loan associations to use "due-on-sale" clauses in mortgage contracts preempts California's prohibition of such clauses). But it is quite another thing for an agency to declare that, even though Congress did not intend to displace state laws that could frustrate full achievement of the federal objectives, the agency has authority to declare that state laws will be preempted on that ground.

When an agency engages in the former action, it is playing the sorcerer's apprentice; when it engages in the latter action, it is improperly playing the sorcerer himself. Put another way, "if Congress does not intend [implied frustration] preemption, Congress should be held not to intend agency [implied frustration] preemption." Nina A. Mendelson, *A Presumption Against Agency Preemption*, 102 NW. U. L. REV. 695, 707 (2008) ("*Agency Preemption*").

For precisely this reason, an agency cannot manufacture preemption by declaring that a standard it has adopted is both a "floor" and a "ceiling." See, *e.g.*, 71 Fed. Reg. at 3935 (FDA's assertion that its labeling requirements "establish both a 'floor' and a 'ceiling'"). Such assertions are invariably followed by the contention that any state measures that impose stricter standards or additional requirements are preempted because they directly conflict with the federal ceiling. See, *e.g.*, U.S. Br. 19. The problem with this approach is that the agency's declaration that its standard is a ceiling is nothing more than a declaration that it is invoking implied frustration preemption.

As Professor Mendelson observes, it is commonplace for agencies to be charged with accomplishing primary goals (*e.g.*, providing a safe workplace, ensuring that drinking water is healthy, making automobiles safer) as well as "countervailing or moderating goals" (*e.g.*, reducing costs to employers, increasing flexibility for manufacturers). *Agency Preemption*, at 709-14. If agencies are allowed to declare their standards to be both floors (to achieve the primary goals) and ceilings (to achieve the countervailing secondary goals), "federal agencies would have the power to preempt nearly any state law operating in the same arena as the federal law." *Id.* at 714. For "[a]n agency can nearly always identify some statutory goal—perhaps opposed to or in tension with the statute's primary goal—with which the state law will conflict." *Id.* at 713; see also *Pension Benefit Guar. Corp. v. LTV Corp.*, 496 U.S. 633, 646 (1990) ("[T]here are numerous federal statutes that could be said to embody countless policies.").

If Congress wishes to grant agencies that massive power, it generally may do so. But where Congress does not express the intent to preempt state laws merely because those laws might frustrate full accomplishment of the federal objective, Congress also did not intend to grant federal agencies the authority to do precisely that under the guise of setting floors and ceilings.

B. In enacting the FDCA, Congress did not express an intent to displace state laws that purportedly frustrate achievement of the statute's objectives.

Because the FDCA lacks an express preemption provision, principles of statutory construction, separation of powers, and federalism weigh heavily against inferring congressional intent to displace state laws with which it is possible to comply. This is not the rare case where frustration preemption should be implied.

Reasonable policy grounds support allowing state tort actions such as Respondent's to proceed; Congress expressly preempted state law with respect to *other* products regulated by the FDA; Congress failed to take express preemptive action notwithstanding the long history of state tort actions against drug manufacturers; and Congress adopted a saving clause in 1962 to limit the FDCA's preemptive scope. All told, Congress's decision not to include an express preemption provision in the FDCA is properly viewed as a decision *not* to displace state tort actions.

1. As explained earlier, if reasonable policy arguments can be asserted both for and against displacement of state law, congressional silence is prop-

erly construed as a decision not to displace state law. That is the situation here.

In *Riegel*, the Court "speculate[d]" that the reason Congress probably wanted the MDA's preemption provision to cover state tort actions was "solicitude for those who would suffer without new medical devices if juries were allowed to apply the tort law of 50 States to all innovations." 128 S. Ct. at 1009. That is a plausible policy justification for preempting state tort actions against prescription drug manufacturers as well. But there are plenty of plausible policy justifications for *not* preempting such actions.

Specifically, Congress may have wanted injured consumers to retain the right to bring tort actions against prescription drug manufacturers:

- to avoid the "harsh implications of foreclosing all judicial recourse for consumers injured" by defective drugs or inadequate drug labels. See Porter, 52 FOOD & DRUG L.J. at 9; *Sprietsma*, 537 U.S. at 64 (state tort actions, "unlike most administrative and legislative regulations[,] necessarily perform an important remedial role in compensating accident victims").

- because tort suits "aid in the exposure of new dangers," which leads manufacturers and federal regulators to address the problems. *Bates*, 544 U.S. at 451.

- based on the concern that "pre-approval testing generally is incapable of detecting adverse effects that occur infrequently, have long latency periods, or affect subpopulations not included or adequately represented in the studies." David Kessler & David C. Vladeck, *A Critical Examina-*

tion of the FDA's Efforts to Preempt Failure-to-Warn Claims, 96 GEO. L.J. 461, 471 (2008).

- based on the concern that the FDA is overworked and underfunded, and therefore cannot ensure that defective and dangerous devices will not reach consumers. See Michael D. Green, *Statutory Compliance and Tort Liability: Examining the Strongest Case*, 30 U. MICH. J.L. REFORM 461, 498-500 (1997).

- based on the concern that the post-approval monitoring system is not up to the task of protecting consumers from drugs whose defects become apparent only after initial FDA approval. See Kessler & Vladeck, 96 GEO. L.J. at 483-95.

In the end, it is for Congress to decide whether the policy considerations noted in *Riegel* outweigh the policy considerations outlined above. Congress's decision not to include an express preemption provision in the FDCA reflects a decision to accept the policy arguments against displacing state tort actions against prescription drug manufacturers.

2. That conclusion is reinforced by Congress's treatment of state law as applied to other products regulated by the FDA. Congress has expressly preempted certain state actions based on injuries arising from medical devices, 21 U.S.C. § 360k(a), and vaccines, 42 U.S.C. §§ 300aa-22(b)(1) and (e); and has preempted state positive-law requirements with respect to over-the-counter drugs, 21 U.S.C. § 379r(a). Congress's decision not to enact a provision expressly preempting state actions against prescription drug companies is therefore telling.

We noted earlier the principle that "where Congress includes particular language in one section of a

statute but omits it in another section of the same Act, it is generally presumed that Congress acts intentionally and purposefully in the disparate inclusion or exclusion." *Russello*, 464 U.S. at 23 (internal quotation marks and citations omitted). That principle applies here.

"The long history of tort litigation against manufacturers" of prescription drugs, and Congress's refusal to amend the FDCA in response, "adds force to" the conclusion that Congress did not intend to preempt such litigation. *Bates*, 544 U.S. at 449. As discussed in § I, *supra*, state tort law has operated concurrently with FDA regulation from the beginning. When Congress crafted the preemption provision in the MDA, it was surely aware that "[j]udgments against manufacturers of various FDA-approved products were by no means rare." Leflar & Adler, 64 TENN. L. REV. at 704. Nevertheless, Congress opted to preempt only state requirements with respect to medical devices—*not* state requirements with respect to drugs. As this Court observed in *Bonito Boats, Inc. v. Thunder Craft Boats, Inc.*, "[t]he case for federal pre-emption is particularly weak where Congress has indicated its awareness of the operation of state law in a field of federal interest, and has nonetheless decided to stand by both concepts and to tolerate whatever tension there is between them." 489 U.S. 141, 166-67 (1989) (internal quotation omitted).

3. Finally, the saving clause adopted as part of the 1962 Amendments to the FDCA confirms that the statute does not impliedly preempt state law. The provision states:

> Nothing in the amendments made by this Act to the Federal Food, Drug, and

> Cosmetic Act shall be construed as invalidating any provision of State law which would be valid in the absence of such amendments unless there is a direct and positive conflict between such amendments and such provision of state law.

Pub. L. No. 87-781, § 202, 76 Stat. 780, 793 (1962).

As a threshold matter, it bears emphasis that not even Petitioner suggests that Congress adopted § 202 in order to *expand* the statute's preemptive scope. Rather, Congress sought to ensure that the courts would not "construe[]" the statute in an overly preemptive manner. *Id.* The general rule against implied frustration preemption should therefore apply with full force to the FDCA.

Turning to the provision's precise meaning, § 202 is properly read as a declaration that state laws are preempted by the FDCA only under the doctrine of impossibility preemption. Section 202's language was borrowed from a pending piece of legislation, H.R. 3, Establishing Rules of Interpretation for Federal Courts Involving the Doctrine of Federal Preemption. See H.R. Rep. No. 1820, 87th Cong., 2d Sess. (June 13, 1962) ("H.R. 3 Report"). Earlier versions of H.R. 3 had been introduced in the 1950s; the amended version reported favorably out of the House Judiciary Committee in June 1962 provided, in pertinent part, as follows:

> [1] No Act of Congress shall be construed as indicating an intent on the part of Congress to occupy the field in which such Act operates, to the exclusion of all State laws on the same subject matter, unless such

> Act contains an express provision to that effect. [2] No provision of an Act of Congress shall be construed as invalidating a provision of State law which would be valid in the absence of such Act, except to the extent that there is a direct and positive conflict between such provisions so that the two cannot be reconciled or consistently stand together.

H.R. 3 Report, at 13. The first sentence explicitly prohibits courts from invoking implied field preemption. The second sentence goes further, and prohibits courts from impliedly preempting state law unless "there is a direct and positive conflict between" federal and state law.

The House debates with respect to the 1962 FDCA Amendments specifically discussed "H.R. 3 clauses,"[8] and it is plain that the FDCA saving clause (proposed in September 1962) adapted the second sentence of H.R. 3. This background teaches two critical lessons about the meaning of § 202 of the FDCA Amendments.

First, Congress knew how to bar field preemption, and only field preemption, if that was its intent. This is what the first sentence of H.R. 3 did. Second, and relatedly, Congress did not want the FDCA saving clause to address only field preemption. If that was Congress's intent, it would have borrowed the *first* sentence of H.R. 3, not the *second* sentence.

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[8] See 108 Cong. Rec. 21,045, 21,046 (Sept. 27, 1962) (statement of Rep. Smith) ("[w]e have all heard of H.R. 3"); *id.* at 21,047 (statement of Rep. Meader) (noting that recently the judiciary committee has been "careful to insert . . . a little H.R. 3 declaration").

The framers of the 1962 Amendments to the FDCA were concerned that "by giving additional authority to the Food and Drug Administration, we may be striking down existing State laws and interfering with existing State machinery in this field." 108 Cong. Rec. 21,045, 21,047 (Sept. 27, 1962) (statement of Rep. Meader).[9] Although the Amendments did not *expressly* preempt state laws, the concern was that they might be found to *impliedly* do so. The framers therefore inserted the saving clause—borrowed from H.R. 3—to make clear that only if state and federal law truly could not stand together would state law be preempted.

All told, the saving clause represents a powerful indication that Congress disfavored implied preemption altogether. At the very least, it further supports the conclusion that the FDCA is not the rare statute in which Congress intended to preempt state law under the doctrine of implied frustration preemption.

CONCLUSION

The judgment of the Vermont Supreme Court should be affirmed.

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[9] See also 108 Cong. Rec. at 21,056 (statement of Rep. Schenck) ("Many very helpful State laws are in effect; many such laws in some instances are even stronger than Federal laws for the protection of human health in the public interest. We here in the Congress should take no action to interfere with these strong and effective laws already approved by State legislatures and doing very effective work in this important effort to protect and improve human health."); *id.* at 21,083 (statement of Rep. Harris) (saving clause was consistent with his "categorical statement that this legislation did not preempt any State laws and was not so intended").

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v.

DIANA LEVINE,

Respondent.

On Writ of Certiorari to the Vermont Supreme Court

BRIEF OF DRI—THE VOICE OF THE DEFENSE BAR AS *AMICUS CURIAE* IN SUPPORT OF PETITIONER

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INTEREST OF *AMICUS CURIAE* DRI[1]

Amicus curiae DRI—the Voice of the Defense Bar and its members have extensive experience defending litigation implicating the Food and Drug Administration's ("FDA") expert determinations regarding prescription drugs. *Amicus* brings practical insight and real-world experiences with the substantial federal oversight of individual prescription drugs and the threats posed to public health by conflicting state co-regulation through tort law. *Amicus* will not repeat the legal arguments that are well developed by petitioner and other *amici*. Instead, *amicus* focuses the Court's attention on several key practical issues.

Despite the views of the majority below that ensuring patient safety requires state law to supplement federal drug oversight, in fact, lay fact-finders' views of complex scientific data and their focus on the allegedly injured party before them cannot substitute for—and frequently conflict with—FDA's expert determinations with respect to a particular drug. FDA is charged by Congress as the expert federal agency to examine risks and benefits at a population level far broader than the circumstances facing any individual plaintiff. The agency must balance safety across the universe of

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[1] Pursuant to Supreme Court Rule 37.6, *amicus curiae* DRI states that no counsel for any party authored this brief in whole or in part and that no entity or person, aside from *amicus curiae*, its members, and its counsel, made any monetary contribution towards the preparation and submission of this brief. Pursuant to Supreme Court Rule 37.3, counsel of record for all parties have received notice of *amicus curiae*'s intent to file this brief and have consented to the filing of this brief in letters on file with the Clerk's office.

potential patients, ensuring that beneficial drugs not only reach the market, but are accompanied by warnings that are scientifically supported and do not unnecessarily deter beneficial use. FDA considers not only patients who potentially will be harmed by use of the drug, but also patients who benefit from use and patients who would be harmed by the restriction of uses of the drug or the absence of the drug from the market altogether. Because lay fact-finders institutionally lack FDA's perspective, irreconcilable conflicts with FDA's conclusions are unavoidable and effectively allow state law to override federal law in a manner inconsistent with the federal drug system.

Amicus has first-hand familiarity with these conflicts in practice, which set up collisions between FDA decisions and state-law mandates. These conflicts leave regulated entities in an impossible position and threaten public health. Absent preemption, companies have incentives to "overwarn" to protect themselves from the threat of liability, thereby undermining FDA's goal of properly calibrating warnings to achieve optimal use; to curtail innovation; to limit availability or withdraw needed medications already on the market; and to increase prices to self-insure against litigation risks.

DRI is an international organization that includes more than 22,000 attorneys involved in the defense of civil litigation. DRI is committed to enhancing the skills, effectiveness, and professionalism of defense attorneys. Because of this commitment, DRI seeks to address issues germane to defense attorneys and the civil justice system, to promote the role of the defense attorney, to improve the civil justice system, and to preserve the civil jury. DRI has long been a voice in the ongoing effort to make the civil justice system

more fair, efficient, and—where national issues are involved—consistent. To promote these objectives, DRI participates as *amicus* in cases that raise issues of importance to its membership and to the judicial system. Recently, DRI filed an *amicus* brief in *Riegel* v. *Medtronic, Inc.*, 128 S. Ct. 999 (2008).

Here, as in *Riegel*, to allow state tort to second-guess the very expert determinations reached by FDA about what labeling is appropriate for prescription drugs would be to disrupt the efficient and fair administration of justice. Permitting States—and lay fact-finders—to serve as quasi-regulators able to require additional warnings inconsistent with FDA's own judgments creates irreconcilable conflicts with federal law and thwarts the attainment of important public health objectives.

SUMMARY OF THE ARGUMENT

First, the analysis of the court below ignores the drug-specific determinations FDA makes in exercise of its role as the expert federal agency. This error, in turn, overlooks the conflicts with federal law and the impossible situations faced by FDA-regulated entities that arise when jurors are told, as they were here, that even when FDA has determined safety and labeling issues, "we don't rely on the FDA to . . . make the safe[ty] decision" or to determine "the extent to which [a company] should have warned" because "FDA doesn't make the decision, you do." JA 211-12, 217. This approach is demonstrably false and irreconcilable with congressional design.

Second, by permitting such second-guessing through state law, the court below ignores well-established principles recognizing that courts are not well-suited to reevaluate decisions within an agency's expert discretion. Moreover, it poses special dangers

given that lay jurors make poor substitutes for FDA in this context because FDA, as the expert federal agency, must make nuanced scientific judgments and set consistent nationwide policy based on overall societal benefits and risks, rather than those implicated in the case of a single litigant.

Third, the absence of preemption encourages numerous negative effects, including (1) increasing defensive labeling to the detriment of optimal patient care, (2) discouraging manufacturers from bringing needed medications to market for fear of liability, (3) encouraging manufacturers to withdraw needed medications from the United States market even though they are available abroad, and (4) increasing prices for those drugs that remain on the market.

ARGUMENT

I. LITIGATING PRESCRIPTION DRUG LABELING ISSUES FDA ALREADY HAS RESOLVED INTERFERES WITH FDA'S FEDERAL MANDATE AND LEAVES REGULATED ENTITIES IN AN IMPOSSIBLE POSITION.

Unacknowledged in the opinion below are the scope and depth of federal regulation to which prescription drugs are subjected under FDA's federal mandate. Cf. Pet. App. 5a; *id.* at 17a. Where (as here) FDA has addressed a specific risk issue, state-law efforts to supplant that determination conflict with FDA's federal mandate and interfere with its mission. Absent preemption, regulated entities are left in an impossible position between dueling federal and state law obligations.

BEST AVAILABLE COPY

A. FDA, The Expert Federal Agency, Is Charged By Congress With Exclusively And Extensively Regulating Prescription Drugs And Their Risks.

1. Since the Pure Food and Drug Act of 1906, Congress has charged FDA, and its predecessor agencies, with regulating drugs in the United States. The scope of FDA's oversight has increased over time.[2] Through the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. §§ 301 *et seq.* ("FDCA"), Congress has charged FDA as the exclusive "expert agency" to regulate every aspect of prescription drugs. *Weinberger* v. *Hynson, Westcott & Dunning, Inc.*, 412 U.S. 609, 619, 627 (1973); see 21 U.S.C. § 393(b) (requiring FDA to "promote the public health by promptly and efficiently reviewing clinical research and taking appropriate action on the marketing of regulated products in a timely manner" and to "protect the public health by ensuring that . . . drugs are safe and effective" as labeled).

Before a prescription drug may be marketed in the United States, FDA must approve a new drug

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[2] In 1938, federal law first required pre-market applications for new drugs. *See* Federal Food, Drug, and Cosmetic Act, Pub. L. No. 75-717, § 505, 52 Stat. 1040, 1052-53 (1938); *United States* v. *Generix Drug Corp.*, 460 U.S. 453, 458 (1983). In 1962, federal law was expanded to prohibit the distribution of a new drug in interstate commerce unless FDA had affirmatively found the drug safe and effective. *See* Drug Amendments Act of 1962, Pub. L. No. 87-781, sec. 102, § 201, 76 Stat. 780, 781-82; Michael I. Krauss, *Loosening the FDA's Drug Certification Monopoly: Implications for Tort Law and Consumer Welfare*, 4 Geo. Mason L. Rev. 457, 461-62 (1996). Thus, unlike the regulation of most other products, "after 1962 a central regulatory authority, rather than the market choices of suppliers, physicians, and patients, determined which drugs were desirable or undesirable." *Id.* at 462.

application ("NDA"). 21 U.S.C. § 355(a), (b). This approval is granted only after FDA is satisfied that the drug is "safe" and "effective." *Id.* § 355(b)(1). An NDA is the culmination of many years of research and evaluation, including laboratory research, animal testing, and multiple phases of clinical studies. See generally Ctr. for Drug Evaluation and Research ("CDER"), Dep't of Health & Human Servs. ("HHS"), FDA, *The CDER Handbook* 4-20 (1998), *available at* http://www.fda.gov/cder/handbook. An NDA contains thousands of pages of medical, pharmacology, chemistry, biopharmaceutical, and statistical submissions. See *id.* at 19, 21; 21 C.F.R. § 314.50 (outlining required NDA contents).

FDA conducts a "strict and demanding" review of these submissions, *Weinberger*, 412 U.S. at 619, 627, conducting a "comprehensive scientific evaluation of the product's risks and benefits under the conditions of use prescribed, recommended, or suggested in the labeling." FDA, Requirements on Content and Format of Labeling for Human Prescription Drugs and Biological Products, 71 Fed. Reg. 3922, 3934 (Jan. 24, 2006). In so doing, FDA utilizes interdisciplinary teams of internal experts to make the requisite safety and efficacy determinations across a number of complex disciplines. For example, medical officers (mostly physicians) evaluate clinical testing, animal toxicology, and human pharmacology. *CDER Handbook*, *supra*, at 22. Pharmacokineticists analyze how a drug's active ingredients are metabolized. See *id.* at 23. Statisticians assess data underlying studies, study methodology, and whether and how study findings can be extrapolated to nationwide patient populations. *Id.*

In addition, advisory panels of outside scientists provide "wider national expert input" into FDA's drug

approval decisions. *Id.* Panels must include scientists "qualified by training and experience to evaluate the safety and effectiveness of the drugs . . . and . . . to the extent feasible, possess skill and experience in the development, manufacture, or utilization of such drugs." 21 U.S.C. § 355(n)(3). Panelists must possess "diverse expertise in such fields as clinical and administrative medicine, pharmacy, pharmacology, pharmacoeconomics, biological and physical sciences, and other related professions." *Id.* (at least two panelists must be "specialists or have other expertise in the particular disease or condition for which the drug under review is proposed to be indicated"). Panels also must include "a representative of consumer interests, and a representative of interests of the drug manufacturing industry not directly affected by the matter to be brought before the panel." *Id.*

An essential aspect of an NDA submission, and FDA's review, is the proposed product labeling. *Id.* § 355(b)(1)(F). Labeling contains not only basic information about dosage and drug composition, but also detail about the disease or health condition for which the drug is intended, methods of administration, and information about risks. 21 C.F.R. § 201.57. Final approved labeling "communicates the conclusions of FDA['s] review of the data." FDA, Professional Product Labeling, Meeting Notice, 60 Fed. Reg. 52,196, 52,196 (Oct. 5, 1995). It "reflects thorough FDA review of the pertinent scientific evidence and communicates to health care practitioners the agency's formal, authoritative conclusions regarding the conditions under which the product can be used safely and effectively," and accordingly constitutes "[t]he centerpiece of risk management for prescription drugs generally." 71

Fed. Reg. at 3934; see also 21 C.F.R. § 201.56(a) ("labeling must contain a summary of the essential scientific information needed for the safe and effective use of the drug[,] labeling must be informative and accurate and neither promotional in tone nor false or misleading in any particular[,] labeling must be based whenever possible on data derived from human experience").

FDA approves an NDA and draft labeling only after it is satisfied that the applicant has met statutory standards for safety and effectiveness under labeled conditions of use. 21 U.S.C. § 355(d); 21 C.F.R. § 314.105(c). If FDA concludes that these showings are insufficient, or that the labeling "is false or misleading in any particular," then the agency "shall issue an order refusing to approve" the NDA. 21 U.S.C. § 355(d); 21 C.F.R. § 314.125(b).

2. If FDA grants approval, the agency remains active in evaluating the drug's safety and efficacy as labeled, after it reaches the market. The agency has broad powers to revoke approval if new clinical trials or other scientific data reliably demonstrate that the drug no longer offers sufficient assurance of safety or effectiveness as labeled. 21 U.S.C. § 355(e).[3] FDA has asserted authority to require, as a condition of

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[3] FDA has withdrawn or suspended drug approvals on numerous occasions. *See, e.g.*, FDA, *FDA Data on PDUFA Drug Approvals, Safety Withdrawals & New Boxed Warnings, at* http://www.fda.gov/oc/pdufa/FDADrugAppSafetyData_files/NMESafetySumm.html (last visited May 28, 2008) (FDA ordered 11 safety-based withdrawals of drugs whose applications were received between 1993 and 2004). FDA also has requested changes in drug labeling based on post-marketing data on numerous occasions. *See, e.g., id.* ("Black Box" warnings, the most severe type of warning, added to 29 drugs in the same period).

NDA approval, that manufacturers conduct post-marketing studies regarding "risks, benefits, and optimal use." 21 C.F.R. § 312.85; see Charles J. Walsh & Alissa Pyrich, *Rationalizing the Regulation of Prescription Drugs and Medical Devices*, 48 Rutgers L. Rev. 883, 914 n.126 (1996) ("Once comparatively rare, post-marketing surveillance studies—sometimes known as Phase IV testing—have now become the rule."). Additionally, manufacturers are required to review and file reports of "[a]dverse drug experience[s]," broadly defined as "[a]ny adverse event associated with the use of a drug in humans, whether or not considered drug related." 21 C.F.R. § 314.80. Companies also must file regular reports of other field experiences and any information that "might affect the safety, effectiveness, or labeling of the drug." *Id.* § 314.81(b)(2)(i). In addition, citizens may provide their views to FDA for consideration.[4]

Nothing in the FDCA or FDA's interpretations of the statutory and regulatory regime supports the view expressed by the court below that a manufacturer may make "unilateral changes to drug labels whenever [it] believes [the changes] will make the product safer." Pet. App. 13a; *accord* Br. United States on Petition, 2007 WL 4555760, at *12-14

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[4] *See, e.g.*, 21 C.F.R. § 10.30 (establishing process for citizens to petition the agency to "issue, amend, or revoke a regulation [or] order [or] take or refrain from taking any other form of administrative action"); *cf. Henley* v. *FDA*, 873 F. Supp. 776, 780-86 (E.D.N.Y. 1995) (holding FDA did not act arbitrarily or capriciously in denying citizen's petition seeking to require warnings that the drugs in question "'may cause cancer in humans,'" and recognizing that "FDA's determination of what labeling best reflects current scientific information regarding the risks and benefits of [the drugs] involves a high degree of expert scientific analysis"), *aff'd*, 77 F.3d 616 (2d Cir. 1996).

(rejecting view of the court below). To the contrary, "[s]ubstantive changes in labeling . . . are more likely than other changes to affect the agency's previous conclusions about the safety and effectiveness of the drug." FDA, New Drug and Antibiotic Regulations, 50 Fed. Reg. 7452, 7470 (Feb. 22, 1985). Accordingly, in general, post-marketing labeling changes may only be made after FDA approval. See 21 C.F.R. § 314.70(b)(2); see also *id.* § 201.57(c) (outlining criteria for labeling changes). As a narrow exception to this rule, if the manufacturer becomes aware of "newly discovered risks" of sufficient scientific heft, FDA, New Drug and Antibiotic Regulations, 47 Fed. Reg. 46,622, 46,623 (proposed Oct. 19, 1982), it may submit a supplement to the agency while changing the labeling, see 21 C.F.R. § 314.70(c)(6)(iii); FDA, Supplemental Applications Proposing Labeling Changes for Approved Drugs, Biologics, and Medical Devices, 73 Fed. Reg. 2848, 2848 (proposed Jan. 16, 2008) (noting "agency's longstanding view" that changes may be made without prior FDA approval only for "newly acquired information" with "sufficient evidence of a causal association with the drug"). In contrast, where (as here) no newly discovered risks are at issue, the manufacturer must go through the pre-approval process before making a change. See 47 Fed. Reg. at 46,623, 46,625; 73 Fed. Reg. at 2848; *accord* Br. United States on Petition, 2007 WL 4555760, at *14-15 (recognizing no new risk information exists in this record).

Even when a manufacturer believes an immediate change in labeling is appropriate based on newly discovered risk information, FDA still can reject the proposed change based on its review of the science or the regulatory balance it seeks to achieve in the labeling. 21 C.F.R. § 314.70(c)(7). The agency may

order the company to discontinue distribution, *id.*, and the manufacturer may be charged with distributing a "misbranded" drug, 21 U.S.C. § 331(a)-(b); see Br. United States on Petition, 2007 WL 4555760, at *15. A drug is misbranded, *inter alia*, when the "labeling is false or misleading in any particular." 21 U.S.C. § 352(a). Misbranding may occur both where labeling fails to *include* warnings FDA has found warranted, and where the labeling fails to *exclude* warnings that do not meet FDA's standards. See *id.* § 352(a), (f); 73 Fed. Reg. at 2850 ("Federal law governs not only what information must appear in labeling, but also what information may not appear."); *Colacicco* v. *Apotex Inc.*, 521 F.3d 253, 269 (3d Cir. 2008) (holding additional warnings sought by plaintiffs were "without scientific basis" and "would therefore be false and misleading" in violation of federal misbranding law); 71 Fed. Reg. at 3935 ("[A]dditional disclosures of risk information can expose a manufacturer to liability under the [FDCA] if the additional statement is unsubstantiated or otherwise false or misleading.").

"Misbranding" is a "prohibited act" under the FDCA, 21 U.S.C. § 331, and the consequences of misbranding can be considerable, including "serious criminal and civil penalties," *Abbott Labs.* v. *Gardner*, 387 U.S. 136, 153 (1967), *abrogated on other grounds by*, *Califano* v. *Sanders*, 430 U.S. 99 (1977); see 21 U.S.C. § 355(e) (withdrawal); *id.* §§ 332-334 (criminal penalties, injunctions, and seizure). Given these risks, "manufacturers typically consult with the FDA before making a label revision." *In re Bextra & Celebrex Mktg. Sales Pracs. & Prod. Liab. Litig.*, No. 05-1699, 2006 WL 2374742, at *8 (N.D. Cal. Aug. 16, 2006) (Breyer, J.); see Br. United States on Petition, 2007 WL 4555760, at *15 (explaining that "[f]or these

reasons, in practice manufacturers typically consult with FDA before making labeling changes that the manufacturer believes could appropriately be made unilaterally").

3. Recent legislation further enhances and formalizes FDA's already robust post-market powers. See Food and Drug Administration Amendments Act of 2007 ("FDAAA"), Pub. L. No. 110-85, 121 Stat. 823, 823 ("An Act to amend the [FDCA] . . . to enhance the postmarket authorities of the [FDA] with respect to the safety of drugs . . . ."); 73 Fed. Reg. at 2850 (FDAAA "provide[s] streamlined authority for FDA to respond to new and emerging safety information"). For instance, FDAAA expressly authorizes FDA to require "postapproval study or studies of the drug, or a postapproval clinical trial or trials of the drug" to address already-known risks, risk signals, and unexpected risks. 21 U.S.C. § 355(o)(3)(A)-(B). It also enhances FDA's power to require labeling changes based on "new safety information that [it] believes should be included in the labeling." *Id.* § 355(o)(4)(A); *accord* 73 Fed. Reg. at 2850 (FDAAA "confirm[s] that Congress intends FDA to carefully regulate the content of labeling for approved products" and allows FDA "to rapidly amend the labeling").

To fund FDA's expanded drug approval and post-market surveillance, FDAAA also substantially increases existing user fees. See Pub. L. No. 110-85, sec. 103(b), § 736(b), 121 Stat. at 827 (authorizing $392 million in user fees, an increase of $87 million from the previous year).[5] These fees allow FDA to

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[5] Since 1992, the Prescription Drug User Fee Act ("PDUFA") has authorized FDA to collect user fees to increase the speed of NDA review and to expand post-market risk management.

hire more reviewers and engage in even more rigorous post-marketing surveillance. See, *e.g.*, Tomas J. Philipson et al., Nat'l Bureau of Econ. Research, Working Paper No. 11724, *Assessing the Safety and Efficacy of the FDA: The Case of the Prescription Drug User Fee Acts* (Oct. 2005), *available at* http://www.nber.org/papers/w11724 (finding user fee regime saves 124,000 to 254,000 life-years).

In implementing FDAAA, FDA recently launched the Sentinel System, "a national, integrated, electronic system for monitoring medical product safety." FDA, *Sentinel System to Monitor Medical Product Safety* (May 22, 2008), *available at* http://www.fda.gov/consumer/updates/sentinel052208.pdf. This system further expands agency access to databases run by private health plans, insurers, and government agencies, thereby enhancing its ability to observe and respond to potential safety issues. See FDA, *The Sentinel Initiative: National Strategy for Monitoring Medical Product Safety* 4, 18-24 (May 2008), *available at* http://www.fda.gov/oc/initiatives/advance/reports/report0508.pdf; News Release, HHS, New Efforts to Help Improve Medical Products for Patient Safety and Quality of Medical Care (May 22,

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Andrew C. von Eschenbach, *Commissioner's Report of FDA, HHS, FY 2006 Performance Report to the President and the Congress for PDUFA* (2006) *available at* www.fda.gov/ope/pdufa/report2006/PDUFA2006perf.pdf. FDA reports that user fees have been "instrumental in new drugs reaching consumers in a timelier manner" and are "essential to maintain the resources required to sustain the advances made in FDA review performance." *Id.* PDUFA has been reauthorized three times by Congress with overwhelming support. *See, e.g.*, H.R. Res. 3580, 110th Cong. (2007); 153 Cong. Rec. H10599 (daily ed. Sept. 19, 2007) (third reauthorization passes House 405-7); 153 Cong. Rec. S11841 (daily ed. Sept. 20, 2007) (third reauthorization passes Senate by unanimous consent).

2008), *available at* http://www.hhs.gov/news/press/2008pres/05/20080522a.html (system enhances "proactive surveillance of medical products on the market").

B. FDA's Determinations About Individual Prescription Drugs Make Conflicts With State Law Inevitable.

Applied to individual drugs, these regulatory principles require a series of delicate public health calibrations by FDA. "FDA is challenged to make sure that it consistently balances access and innovation against the steps taken to improve [its] approach to safety issues." FDA, *The Future of Drug Safety—Promoting and Protecting the Health of the Public: FDA's Response to the Institute of Medicine's 2006 Report* 3 (Jan. 2007), *available at* http://www.fda.gov/oc/reports/iom013007.pdf. FDA's dual mission—minimizing risks *and* facilitating access—necessarily involves the exercise of expert judgment because every drug has risks. See 21 U.S.C. § 393(b).

To fulfill its mission, FDA must make labeling decisions regarding individual drugs that require the agency to rely on its expertise and knowledge of the total public health picture. The agency makes a "comprehensive scientific evaluation of the product's risks and benefits *under the conditions of use*"—not in the "abstract." 71 Fed. Reg. at 3934 (emphasis added). For instance, the agency may be willing to tolerate significant risks when a drug may be the only viable treatment for a life-threatening condition. See *United States* v. *Rutherford*, 442 U.S. 544, 556-57 (1979) (recognizing that the balance the agency seeks to strike between effectiveness and safety may vary according to the condition the drug is intended to treat); *accord* Br. United States on Petition, 2007 WL 4555760, at *10 (FDA has approved "highly toxic"

and "not 'safe'" cancer treatments "because the potential benefits to health outweigh the risks"); 21 C.F.R. pt. 314 subpt. H.

These dynamics translate directly into FDA's determinations about proper drug labeling. The agency must craft balanced labeling that both ensures prescribing physicians understand the dangers of the medication and its benefits, thereby allowing them to select the proper course of treatment for individual patients, without overwhelming them with low-risk information that undermines rational prescribing. As FDA has explained, "[o]verwarning, just like underwarning, can . . . have a negative effect on patient safety and public health" because "theoretical hazards not well-grounded in scientific evidence can cause meaningful risk information to lose its significance." 71 Fed. Reg. at 3935 (internal quotation omitted).

In reaching these decisions, FDA must exercise its considerable expertise and discretion to reach the decision it finds most appropriate in light of all the circumstances. *Id.* at 3934 (FDA considers "important and practical public health issues pertaining to the use of the product in day-to-day clinical practice"). As part of this process, there may be a divergence of opinion among FDA reviewers. FDA, *Guidance: Drug Safety Information—FDA's Communication to the Public* 4 (Mar. 2007), *available at* http://www.fda.gov/CDER/guidance/7477fnl.pdf (acting on emerging risks is "a matter of judgment, about which reasonable people with relevant experience may disagree"). For instance, a medical officer may recommend one course of action based on her review in a given discipline that the agency ultimately disagrees with after reviewing the entire picture. Likewise, advisory boards may have

dissenting voices and sometimes recommend action the agency ultimately rejects. See Richard A. Merrill, *The Architecture of Government Regulation of Medical Products*, 82 Va. L. Rev. 1753, 1781 n.86 (1996) (although FDA "usually accepts [advisory committee advice] regarding the approval of new drugs[,] [a]n advisory committee can, and some occasionally do, disagree with the assessment of the agency's own reviewers about the approvability of a drug"). To achieve the goals of the FDCA, however, final decisions which will guide drug availability, labeling, and use nationwide ultimately must be reached by the agency. Cf. *id.* ("these committees offer only advice; they do not make decisions"). The highly deferential FDCA scheme designed by Congress necessarily means that, in the end, FDA alone must decide and strike these balances.

Where, as here, state law runs headlong into the federal agency's judgment, the regulated entity faces an inevitable Catch-22. Its products may not reach or remain on the market if it fails to abide by FDA's judgments or if it substitutes its own views of the science and proper labeling for that of the agency. The company also faces the prospect of federal penalties should it decide to distribute a misbranded drug in its effort to avoid state-law liability. On the other hand, engaging in federally approved conduct that is found to violate state law makes the regulated entity's product a magnet for state-law litigation. Yet, absent preemption, when FDA has made a determination about whether a drug should come to market, and has addressed a particular risk issue, state-law efforts will be permitted to override the expert agency's determinations.

II. JUDGES AND JURIES ARE NOT PROPERLY EQUIPPED TO MAKE THE JUDGMENTS CONGRESS DELEGATED TO THE EXPERT AGENCY.

As difficult as it may be for FDA to calibrate the right balance in a particular case, it is practically impossible for courts and juries to do so given that they lack the agency's knowledge and expertise, as well as its perspective.

A. Courts Routinely Defer To Expert Regulators.

Congressional design requires federal courts—never mind state law and state lay juries—to accept and defer to FDA's expert judgment and exercise of discretion about such difficult issues. See, *e.g.*, *Brandenfels* v. *Heckler*, 716 F.2d 553, 555 (9th Cir. 1983) ("Determining reliable scientific data is not the judicial function. Congress vested that responsibility in the FDA and we will not preempt its presumed expertise."); *Premo Pharm. Labs., Inc.* v. *United States*, 629 F.2d 795, 803 (2d Cir. 1980) ("FDA . . . as distinguished from a court, possesses superior expertise, usually of a complex scientific nature"); see also *Slater* v. *Optical Radiation Corp.*, 961 F.2d 1330, 1333 (7th Cir. 1992) (Posner, J.) (observing that "FDA decided, *whether rightly or wrongly*" that a product should come to market with certain warning, "but pursuant to regulations the validity of which the plaintiff does not question," plaintiffs' claims invite "a direct collision with federal policy") (emphasis added); cf. *Heckler* v. *Chaney*, 470 U.S. 821, 837-38 (1985) (holding that FDA's decisions regarding enforcement of FDCA are not subject to judicial review). Indeed, the Court has observed that "[i]t is enough for us that the expert agency . . . has determined that such regulation is desirable for the public health, for we

are hardly qualified to second-guess the Secretary's medical judgment." *United States* v. *An Article of Drug . . . Bacto-Unidisk . . .*, 394 U.S. 784, 791-92 (1969).

These principles, of course, are consistent with a body of this Court's precedents in related contexts which admonish courts not to second-guess decisions within an agency's expert discretion. As the Court explained in *United States* v. *Varig Airlines*, 467 U.S. 797 (1984), for instance:

> Decisions as to the manner of enforcing regulations directly affect the feasibility and practicality of the Government's regulatory program; such decisions require the agency to establish priorities for the accomplishment of its policy objectives by balancing the objectives sought to be obtained against such practical considerations . . . . Judicial intervention in such decisionmaking through private tort suits would require the courts to "second-guess" the political, social, and economic judgments of an agency exercising its regulatory function.

Id. at 820; see, *e.g.*, *Mobile Oil Exploration & Producing S.E. Inc.* v. *United Distrib. Cos.*, 498 U.S. 211, 231 (1991) ("We are neither inclined nor prepared to second-guess the agency's reasoned determination in this complex area."); *American Textile Mfgs. Inst., Inc.* v. *Donovan*, 452 U.S. 490, 523 (1981) ("'the possibility of drawing two inconsistent conclusions from the evidence does not prevent an administrative agency's finding from being supported by substantial evidence'") (citation omitted).[6]

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[6] *See also, e.g.*, *Sierra Club* v. *EPA*, 353 F.3d 976, 992 (D.C. Cir. 2004) ("We will not second-guess the agency's weighing of costs and benefits.") (Roberts, J.) (internal quotation and

Given the recognition that federal courts should not second-guess complex federal agency determinations, as addressed next, the risks associated with having state fact-finders rebalance or reject FDA's determinations under color of state law is even greater. And where, as here, a state ruling speculates why the agency acted as it did as a means to overrule FDA's decisions, the conflict and interference with the agency's functions are particularly acute. See Pet. App. 4a-5a (viewing FDA's "'brief comment[s]'" as insufficient to support its determinations).

B. Juries Are Poor Substitutes For FDA In This Context.

A dramatic gulf separates the competence of FDA from that of state jurors who, absent preemption, are called on to "police" prescription drugs and second-guess federal regulators. Laypersons applying state law cannot substitute for FDA, the expert agency congressionally delegated the role of meticulously balancing nuanced and sometimes competing nationwide goals. FDA's regulation of prescription drugs is, as shown above, governed by a sweeping network of federal law individually applied to each

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alteration omitted); *Southwestern Pa. Growth Alliance* v. *Browner*, 121 F.3d 106, 117 (3d Cir. 1997) (Alito, J.) ("It is not the role of a reviewing court to second-guess the scientific judgments of the [agency].") (internal quotation omitted); *United Steelworkers of Am.* v. *Marshall*, 647 F.2d 1189, 1206-07 (D.C. Cir. 1980) (Wright, J.) (recognizing that agency decisions turn on "inferences from complex scientific and factual data," and "we do not pretend to have the competence or the jurisdiction to resolve technical controversies in the record"); *id.* at 1263 ("Where the agency presents scientifically respectable evidence which the petitioner can continually dispute with rival . . . evidence . . . the court must not second-guess the particular way the agency chooses to weigh the conflicting evidence or resolve the dispute.").

drug. A lay jury lacks the expertise and the broader perspective of FDA and thus cannot adequately adjudicate individual patient risks in the context of population benefits—quintessentially the kind of issue FDA must confront every day. Without preemption, however, state juries are asked to do just that. See, *e.g.*, Pet. Br. 23 ("'Thank God we don't rely on the FDA to . . . make the safe[ty] decision. You will make the decision.'") (quoting JA 211).

As detailed above, FDA determinations about how best to regulate a specific drug and its labeling are highly complex. See generally, *e.g.*, *Henley* v. *FDA*, 77 F.3d 616, 620 (2d Cir. 1996) ("FDA's determination of what labeling best reflects current scientific information regarding the risks and benefits of [a drug] involves a high degree of expert scientific analysis.") (internal quotation omitted); see *supra* § I. When these issues are put to a jury, the risk of error is high. Not only do jurors lack scientific and regulatory expertise, they lack the comprehensive data necessary to assess individual patient risks in the light of the benefits a drug confers on the larger population.

As a general matter,

> the tort system, as part of a larger regulatory scheme, is best equipped to handle products or services *that do not involve intrinsic risks*, which can be predicted and regulated beforehand by legislatures, but that encompass episodic risks or faulty behavior that can only be detected after-the-fact by those personally affected by such behavior.

Alan L. Calnan, *Distributive & Corrective Justice Issues In Contemporary Tobacco Litigation*, 27 Sw. U. L. Rev. 577, 636 (1998) (emphasis added). Thus, in

prescription drug cases, which by definition involve inherent risks, juries are particularly poor substitutes for federal regulators.

Jurors also lack the nationwide perspective FDA brings to its extensive regulation of prescription drugs. As Judge Easterbrook has explained: "Jurors see today's injury; persons who would be injured if [the product were not on the market as constituted] are invisible. Although witnesses may talk about them, they are spectral figures, insubstantial compared to the injured plaintiff, who appears in the flesh." *Carroll* v. *Otis Elevator Co.*, 896 F.2d 210, 216 (7th Cir. 1990) (Easterbrook, J., concurring). A further complication is that jurors may be "prone to hindsight bias, believing that an event that has already occurred was more likely to have happened than was true *ex ante* and could have been foreseen." Hugo M. Mialon & Paul H. Rubin, *The Economics of the Bill of Rights*, 10 Am. L. & Econ. Rev. 1, app. B at 54 (2008).

Whereas FDA evaluates the risks of harm against the benefits of use in the overall population, jurors may tend to "over-assess low-probability events and are particularly likely to focus on the worst-case scenario." W. Kip Viscusi, *Jurors, Judges, and the Mistreatment of Risk by the Courts*, 30 J. Legal Stud. 107, 111 (2001); *id.* at 111-15; see also W. Kip Viscusi, *Corporate Risk Analysis: A Reckless Act?*, 52 Stan. L. Rev. 547, 588 (2000) (explaining that some jurors believe cost-benefit assessments are improper).

As Justice Breyer stated to plaintiffs' counsel during a recent oral argument:

> You came up and began and said this drug has side effects that hurt people. And that's a risk

> when you have a drug, and it's a terrible thing if the drug hurts people.
>
> There's a risk on the other side. There are people who are dying or seriously sick, and if you don't get the drug to them they die. So there's a problem. You've got to get drugs to people and at the same time the drug can't hurt them.
>
> Now, *who would you rather have make the decision as to whether this drug is, on balance, going to save people or, on balance, going to hurt people? An expert agency, on the one hand, or 12 people pulled randomly for a jury rol[l] who see before them only the people whom the drug hurt and don't see those people who need the drug to cure them?*

Warner-Lambert Co. v. *Kent*, No. 06-1498, 2008 WL 495030, at *30 (U.S. Feb. 25, 2008) (emphasis added). In the same vein, "[a]pplication of broad liability rules and the application of 20-20 hindsight often places juries in the position of second guessing the FDA on the types of warnings that should be provided with prescription drug products and which products should be marketed. Too often these judgments collide." W. Kip Viscusi et al., *Deterring Inefficient Pharmaceutical Litigation: An Economic Rationale for the FDA Regulatory Compliance Defense*, 24 Seton Hall L. Rev. 1437, 1467-68 (1994); see, *e.g.*, David R. Geiger & Mark D. Rosen, *Rationalizing Product Liability for Prescription Drugs: Implied Preemption, Federal Common Law, and Other Paths to Uniform Pharmaceutical Safety Standards*, 45 DePaul L. Rev. 395, 396-97 (1996) (discussing "retrospective jury nullification" of FDA regulations being "contrary to public policy").

Whereas jurors not only lack a sense of the overall regulatory policy a statutory scheme seeks to achieve, and "may become fixated on awarding compensation to the needy plaintiff put before them," FDA's determinations can and must "tak[e] a broader view of the inevitable tradeoffs involved in specifying appropriate product designs and disclosures of risk information." Lars Noah, *Rewarding Regulatory Compliance: The Pursuit of Symmetry in Products Liability*, 88 Geo. L.J. 2147, 2163 (2000). In sum, jury trials do not permit lay fact-finders to see the overall picture FDA must consider when striking the proper balance in regulating a particular drug. When a jury's view is substituted for FDA's, as the court below allowed, a core aspect of the federal regulatory scheme—one critical to innovation and overall public health benefits—is lost.

C. Experience Shows That, Absent Preemption, Lay Fact-finders May Disrupt The Careful Balances Struck By FDA.

Recently, and with seemingly increasing frequency, plaintiffs have sought to recalibrate through state law FDA's decisions about the presentation of risk information in labeling, among other agency determinations under the FDCA. Where, as here, plaintiffs' claims ask a jury applying state law to pass on the very issues addressed by FDA under federal law, those claims amount to a frontal attack on FDA's regulatory authority. State-law liability also results in a disparate state-by-state hodgepodge of duties and creates unavoidable conflicts as manufacturers attempt simultaneously to satisfy state and federal law. Recent cases illustrate the point.

1. Litigation over warnings in labeling for antidepressant drugs known as selective serotonin reuptake inhibitors ("SSRIs") illustrates the

importance of expert oversight in regulating prescription drugs, including how FDA's study of risk may unfold, how FDA ensures risk information is supported by reliable science, and how the agency provides risk information provided to prescribing physicians through labeling without improperly discouraging the use of these important products. They also demonstrate how state law threatens these federal determinations.

The main state-law claim in the SSRI litigation is that manufacturers should be held liable because "the drugs' labeling failed to warn of their association with an increased risk of suicidality" in adults. *E.g.*, *Colacicco*, 521 F.3d at 256.[7] FDA repeatedly has reviewed this risk. See *id.* at 269. In 1991, after evaluating whether SSRIs "caused or intensified suicidal thoughts," FDA's Psychopharmacological Drugs Advisory Committee concluded that "no" suicidality warning should be added to the labeling for SSRIs. *Id.*; see *Dobbs* v. *Wyeth Pharms.*, 530 F. Supp. 2d 1275, 1282-83 (W.D. Okla. 2008). Thereafter, FDA rejected citizen petitions seeking to withdraw approval "as a result of its asserted association with suicide or to include a suicide warning on the labeling of [the] drug," concluding that scientific evidence did not support this action. *Colacicco*, 521 F.3d at 269; see *Dobbs*, 530 F. Supp. 2d at 1282-83. See also *Colacicco*, 521 F.3d at 270

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[7] *Accord Dobbs* v. *Wyeth Pharms.*, 530 F. Supp. 2d 1275, 1277 (W.D. Okla. 2008); *Tucker* v. *SmithKline Beecham Corp.*, No. 1:04-cv-1748-DFH-WTL, 2007 WL 2726259, at *1 (S.D. Ind. Sept. 19, 2007); *Estates of Tobin ex rel. Tobin* v. *SmithKline Beecham Pharms.*, 164 F. Supp. 2d 1278, 1287 (D. Wyo. 2001); *Motus* v. *Pfizer Inc.*, 127 F. Supp. 2d 1085, 1086-87 (C.D. Cal. 2000).

(*amicus* briefs reiterating this point); *Dobbs*, 530 F. Supp. 2d at 1283-84 (same).

In late 2003, FDA issued a Public Health Advisory regarding increased suicidality in *pediatric* users of antidepressants and reaffirmed that there was "'no evidence'" of increased suicidality in adults. *Colacicco*, 521 F.3d at 270. In 2004, FDA conducted further studies on pediatric suicidality, finding a "causal link between the use of antidepressants and suicidality in pediatric patients," and adding a black box warning to SSRI labeling regarding pediatric use. *Tucker* v. *SmithKline Beecham Corp.*, No. 1:04-cv-1748-DFH-WTL, 2007 WL 2726259, at *3 (S.D. Ind. Sept. 19, 2007); *Colacicco*, 521 F.3d at 270-71. FDA also reviewed whether there was any increased risk in adults despite its earlier findings to the contrary. *Tucker*, 2007 WL 2726259, at *4. In 2007, it concluded that there was an increased risk of suicidality in "'children, adolescents, and young adults'" taking antidepressants, *Dobbs*, 530 F. Supp. 2d at 1284, but *no* increased risk in adults beyond age 24; indeed, "there was a reduction in risk with antidepressants compared to placebo in adults aged 65 or older," *Tucker*, 2007 WL 2726259, at *4.

Despite FDA's determinations, lawsuits nationwide have asked courts and juries to reach contrary determinations under state law. Many courts have rejected these claims on the basis of preemption. See, *e.g.*, *Colacicco*, 251 F.3d at 271; *Dobbs*, 530 F. Supp. 2d at 1290 ("the label warning that Plaintiff seeks to require has been considered and rejected by the FDA; therefore, Defendant would face conflicting obligations under Oklahoma and federal law") (footnote omitted); *Tucker*, 2007 WL 2726259, at *10. Nonetheless, other courts have allowed claims to survive summary judgment, see *Motus* v. *Pfizer Inc.*,

127 F. Supp. 2d 1085, 1092-1100 (C.D. Cal. 2000), and even to serve as the basis for substantial jury awards, see *Estates of Tobin ex rel. Tobin* v. *SmithKline Beecham Pharms.*, 164 F. Supp. 2d 1278, 1280-81, 1283-84 (D. Wyo. 2001) (upholding $6 million jury award because "the absence of warnings" regarding adult suicidality "proximately caused the murders and suicide in this case"). Indeed, the *Tobin* court permitted a multi-million dollar verdict based on the notion that SSRI use caused a murder-suicide even though the individual who allegedly killed himself and murdered his family was 60 years old—the very age group FDA had concluded has *no* increased risk of suicidality from SSRIs. See *Paxil Maker Ordered to Pay $8 Million: Jury Says Anti-Depressant Largely to Blame for Deadly Shooting Spree*, AP Online, June 6, 2001.

These outcomes cannot be squared with FDA's scientific determinations and its role as the expert agency under the FDCA. When a lay jury is permitted to substitute its own conclusions for that of the agency, certainty is undermined and the most restrictive state laws effectively commandeer the regulatory scheme.

2. These dangers are not limited to one set of cases. As FDA has recognized, state-law claims seeking to overturn FDA's expert determinations have been brought with respect to many products and "have directly threatened the agency's ability to regulate manufacturer dissemination of risk information for prescription drugs in accordance with the act." 71 Fed. Reg. at 3934 (citing cases).

In *Dowhal* v. *SmithKline Beecham Consumer Healthcare*, 88 P.3d 1 (Cal. 2004), for example, FDA rejected a manufacturer's proposed warning on nicotine replacement therapy ("NRT") products

regarding potential birth defects or reproductive harm, as well as a citizen petition requesting additional warnings about fetal risks. *Id.* at 5-6. Nonetheless, the same individual who filed the citizen's petition also brought state-law claims against the manufacturer for failing to provide these same warnings. *See id.* at 9. Although the intermediate appellate court allowed the suit to proceed, the California Supreme Court reversed, holding federal preemption barred the claims given

> the FDA[-approved] warning serv[ed] a nuanced goal—to inform women of the risks of NRT products, but in a way that will not lead some women, overly concerned about those risks, to continue smoking. This creates a conflict with the state's more single-minded goal of informing the consumer of the risks.

Id. at 15.

Had the claims been permitted, as the lower court allowed, FDA's expert determination about what warning was required (and prohibited) under federal law could not be reconciled with a verdict for the plaintiff. The defendant would have faced impossible decisions about how to market its product: the warning required by state law would require it to violate federal law, contrary to the "nuanced goals" reflected in the agency's decision.

III. "REGULATING" DRUG LABELING THROUGH STATE LAW UNDERMINES THE PURPOSES OF THE FDCA AND HARMS PUBLIC HEALTH.

In addition to undermining FDA's judgment in a particular case and leaving regulated entities in an untenable position about whether to follow conflicting federal or state law, state-law efforts to impose

liability have a number of negative effects on federal public health objectives. These effects include: irrational prescribing due to defensive labeling, decreased innovation, decreased availability of existing treatments, and increased price.

1. First, FDA has recognized that state law liability for failure to warn creates an incentive for drug companies to engage in "'defensive labeling.'" 71 Fed. Reg. at 3934-35 (such lawsuits "can lead to labeling that does not accurately portray a product's risks, thereby potentially discouraging safe and effective use of approved products or encouraging inappropriate use and undermining the objectives of [the FDCA]"); accord Br. *Amicus Curiae* U.S. at *25-26, *Horn* v. *Thoratec* (filed 3d Cir. May 14, 2004) ("*Horn* Br."), *available at* 2004 WL 1143720. Defensive labeling can include unwarranted contraindications, as the plaintiff sought in this case, as well as other risk-adverse information and "scientifically unsubstantiated warnings," which cause physicians to misapprehend the relationship "of benefits and risks" that they rely on "to make appropriate judgments about drug use." 71 Fed. Reg. at 3935. As a result, beneficial drugs may be underutilized out of unwarranted fears or may be used when they should not be because physicians cannot distinguish the defensive labeling from the unsubstantiated risks. See *id.*; *Horn* Br., at *25-26; see generally W. Kip Viscusi, *Individual Rationality, Hazard Warnings, and the Foundations of Tort Law*, 48 Rutgers L. Rev. 625, 665-66 (1996) ("Excessive warnings are not innocuous. . . . [I]f warnings are included for inconsequential risks, they will serve to further dilute the warnings for the real hazards that should be identified to consumers.").

Crowding the warning label with a cacophony of unsubstantiated risk information also is directly contrary to regulations promulgated by FDA in 2006 which sought to make labeling easier for prescribers to understand by highlighting what the agency determines is the most important risk information. See 21 C.F.R. § 201.57(a) (discussing "Highlights of Prescribing Information" section of labeling). The Highlights section includes the most important risk information and, by design, excludes less important risk information. Highlights includes, for example, "[a] concise summary of the most clinically significant [risk] information" and recommendations for patient monitoring and other "measures that can be taken to prevent or mitigate harm." *Id.* § 201.57(a)(10); see *id.* § 201.57(a)(11) (requiring "[a] list of the most frequently occurring adverse reactions").

As FDA recognized when the Highlights regulation was issued, "[p]hysicians, pharmacists, other health care practitioners, health care advocacy groups, and professional societies and organizations representing health care practitioners expressed unequivocal enthusiasm about and uniform support for Highlights." 71 Fed. Reg. at 3930. Although FDA concluded that this provision "is a vital component of the efforts to reduce the numbers of adverse reactions from medication errors due to misunderstood or incorrectly applied drug information," the proliferation of defensive labeling would erode those advances, and thus harm FDA's core public health mission. *Id.* at 3931.

Thus, even where FDA exercises the utmost care in attempting to balance patient safety while encouraging necessary use of beneficial medications, heightened warnings may have unintended adverse consequences. In a situation where warnings above

and beyond those desired by FDA are being issued, the negative consequences of overdeterrence should be expected to increase.

2. Second, state tort liability encourages companies to halt development of promising new products. This consequence of the current liability situation clashes with a central aspect of FDA's mission: to encourage development of innovative drugs.

If state law imposes substantial liability on a manufacturer for doing just what FDA commanded it to do—as the court below allowed here—there is a perverse incentive for the manufacturer to cease innovation, particularly for drugs that are the least profitable or pose the highest degree of risk. See, *e.g.*, *Browning Ferris Indus. of Vt., Inc.* v. *Kelco Disposal, Inc.*, 492 U.S. 257, 282 (1989) (O'Connor, J., concurring in part and dissenting in part) (observing that "threat of . . . enormous awards" has convinced prescription drug manufacturers "that it is better to avoid uncertain liability than to introduce a new pill"); *Carlin* v. *Superior Court*, 920 P.2d 1347, 1361 (Cal. 1996) ("the imposition of excessive liability on prescription drug manufacturers may discourage the development and availability of life-sustaining and lifesaving drugs"). Absent preemption of appropriate claims, drug companies are left with few choices about how to structure their conduct to avoid liability. See Margaret Gilhooley, *Innovative Drugs, Products Liability, Regulatory Compliance, and Patient Choice*, 24 Seton Hall L. Rev. 1481, 1483-84 (1994) ("[M]edical experts have expressed concern that *uncertain liability standards*, coupled with litigation costs, may discourage useful drug innovation.") (emphasis added).

The easiest way to prevent unwarranted litigation may be to avoid market participation altogether, except where the potential benefits are massive. See FDA, *Innovation or Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products* (Mar. 2004), *available at* http://www.fda.gov/oc/initiatives/criticalpath/whitepaper.html ("[I]nnovators often concentrate their efforts on products with potentially high market return."); Michael Freedman, *The Tort Mess*, Forbes, May 13, 2002, *available at* http://www.forbes.com/forbes/2002/0513/090.html ("[D]rug companies are willing to take on the risk of lawsuits in marketing blockbusters . . . . [,] [b]ut in other cases the chance of liability is too great. . . . Companies also limit research on orphan drugs—those that cure rare, often fatal illnesses—because the potential tort liability outweighs the profit potential.").

3. Similarly, the threat of state-law liability for complying with FDA's determinations creates incentives for manufacturers to restrict drug uses or to withdraw approved drugs from the market. See, *e.g.*, Howard A. Denemark, *Improving Litigation Against Drug Manufacturers for Failure to Warn Against Possible Side-effects: Keeping Dubious Lawsuits from Driving Good Drugs Off the Market*, 40 Case W. Res. L. Rev. 413, 413 (1989-90) ("Beneficial drugs, approved by [FDA], have been forced off the market by the current legal standards for imposing a duty on drug manufacturers to warn of adverse side-effects from their drugs.") (emphasis omitted).

This phenomenon has been observed, for example, in the area of reproductive health. See S. Rep. No. 105-32, at 7 (1997) ("'Liability concerns are keeping products, which have already been developed, off the market despite a known therapeutic need.'") (citation

omitted). In perhaps the most famous example, Bendectin, the only FDA-approved medication for treating morning sickness, was beset by thousands of tort suits alleging birth defects even though no scientifically reliable study ever validated this connection, and FDA formally determined that Bendectin did not present this risk. See Louis Lasagna, *The Chilling Effect of Product Liability on New Drug Developments, in The Liability Maze* 334, 337-41 (P.W. Huber & R.E. Litan eds., 1991); FDA, Determination that Bendectin Was Not Withdrawn From Sale For Reasons of Safety or Effectiveness, 64 Fed. Reg. 43,190 (Aug. 9, 1999); *Daubert* v. *Merrell Dow Pharms., Inc.*, 509 U.S. 579, 582 (1993). Nonetheless, liability fears, litigation, and insurance costs prompted the manufacturer to withdraw the drug from the United States market—even though it still is available abroad. See generally Lasagna, *supra*, at 340-41. No substitute has since been developed or FDA-approved, leaving a treatment gap for a serious condition and triggering a substantial increase in related hospitalizations. See *id.*; Jane E. Henney, FDA/NIH Conference, *Clinical Pharmacology During Pregnancy: Addressing Clinical Needs Through Science* (Dec. 4, 2000), *available at* http://www.fda.gov/oc/speeches/2000/nichconference12-4.html.

The birth control drug Norplant also was impacted by the threat of state-law claims. See generally Anna Birenbaum, Note, *Shielding the Masses: How Litigation Changed the Face of Birth Control*, 10 S. Cal. Rev. L. & Women's Stud. 411, 412-13 (2001). Although FDA had found the drug safe and effective and it had millions of users, litigation concerns knocked the drug off the market. See *id.* Women had one less birth control option and companies were

deterred from researching and developing similar products. *Id.* at 413 ("[T]here is no longer an incentive for drug companies to research and market new birth control devices, since the threat of litigation is something that they are keenly aware of in the wake of Norplant."); see generally S. Rep. No. 105-32, at 7 ("'[l]iability concerns are stifling research and development of products for women'") (alteration in original).

4. Finally, even for drugs that make it to and remain on the market, higher prices may be the natural outcome. See, *e.g.*, *Brown* v. *Superior Court*, 751 P.2d 470, 478 (Cal. 1988) (observing that "the consuming public . . . will pay a higher price for the product to reflect the increased expense of insurance to the manufacturer resulting from its greater exposure to liability"); S. Rep. No. 105-32, at 3 ("Increased product liability costs are reflected in dramatic increases in liability insurance costs. Over the last forty years, general liability insurance costs have increased at over four times the rate of growth of the national economy."). Where liability is imposed despite a drug meeting federal standards, the resulting "product price may reflect external costs not associated with the risks of the medication [and] distort the cost-benefit calculus faced by each consumer." Note, *A Question of Competence: The Judicial Role in the Regulation of Pharmaceuticals*, 103 Harv. L. Rev. 773, 780-81 (1990).

Absent preemption, there is a substantial risk of these adverse consequences, each of which would be contrary to the FDCA's purposes.

CONCLUSION

For these reasons, and those stated in petitioner's brief, the judgment of the Vermont Supreme Court should be reversed.

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IN THE

Supreme Court of the United States

WYETH,

Petitioner,

v.

DIANA LEVINE,

Respondents.

On Writ of Certiorari to the Supreme Court of Vermont

BRIEF OF WASHINGTON LEGAL FOUNDATION AND AMERICAN COLLEGE OF EMERGENCY PHYSICIANS AS *AMICI CURIAE* IN SUPPORT OF PETITIONER

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INTERESTS OF *AMICI CURIAE*[1]

The Washington Legal Foundation ("WLF") is a non-profit, public-interest law and policy center based in Washington, D.C., with supporters in all 50 states. WLF devotes a substantial portion of its resources to defending free enterprise principles, individual rights, a limited and accountable government, and the proper use of our state and federal judicial systems. To that end, WLF has frequently appeared as *amicus curiae* in this and other federal courts in cases involving preemption issues, to point out the economic inefficiencies often created when multiple layers of government seek simultaneously to regulate the same business activity. *See, e.g., Riegel v. Medtronic, Inc.*, 128 S. Ct. 999 (2008); *Bates v. Dow Agrosciences LLC*, 544 U.S. 431 (2005); *Geier v. Am. Honda Motor Co.*, 529 U.S. 861 (2000); *United States v. Locke*, 529 U.S. 89 (2000).

WLF is particularly concerned that individual freedom, the American economy, and the public health and welfare suffer when state law, including state tort law, imposes upon industry an unnecessary layer of regulation that frustrates the objectives or operation of specific federal regulatory regimes, such as the Federal Food, Drug, and Cosmetic Act (FDCA) at issue here.

The American College of Emergency Physicians ("ACEP") is a nonprofit, voluntary professional and educational society of over 26,000 emergency physicians

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[1] *Amici* hereby affirm that no counsel for either party authored any part of this brief, and that no person or entity other than *amici curiae* and their counsel provided financial support for the preparation and submission of this brief. All parties have consented to the filing of this brief; blanket letters of consent have been lodged with the clerk.

practicing in the United States and other countries. Founded in 1968, ACEP is the nation's oldest and largest association of emergency physicians. ACEP fosters the highest quality of emergency medical care through the education of emergency physicians, other health care professionals, and the public; the promotion of research; the development and promotion of public health and safety initiatives; and the provision of leadership in the development of health care policy.

ACEP submits this *amicus* brief on behalf of its physician members and in the interest of their patients on the basis that appropriate medical care is best determined by trained medical professionals providing care pursuant to the scope of practice afforded by their license and in compliance with federal and state regulations.

The *amici* have no direct interest, financial or otherwise, in the outcome of this case. They are filing due solely to their interest in the important issues raised by this case.

INTRODUCTION AND SUMMARY OF ARGUMENT

At issue in this case is whether a lay jury should be allowed to impose a requirement under state tort law that conflicts with the informed judgment of the experts at the federal Food and Drug Administration that physicians should not be foreclosed from using the IV push method of injection of Phenergan as medically-indicated in their patients. The Vermont Supreme Court's decision to allow a state jury to so trump FDA's balanced determination is wrong as a matter of

preemption law under this Court's prior holdings, and it reflects a basic failure to understand the way in which such state tort law requirements can undermine federal objectives in protecting the public health.

Simply stated, in the area of prescription drugs, the argument accepted below that "more" use limitations and warnings are always "better" is fundamentally flawed. FDA's directive to Wyeth on the proper labeling of Phenergan reflected its expert determination that the benefits to the patient population as a whole of a physician option for IV push administration outweighs the adverse outcomes that might arise from human error in individual cases. The jury below could not assess that balancing question. They were not faced with the patients for whom IV push administration might be the only means for effectively receiving needed Phenergan treatment. The jury's decision, in sharp contrast to that of FDA, could not and did not take those other patients' wellbeing into account. This case highlights the reality that properly guides FDA's decision making on the labeling of prescription drugs: use limitations and warnings do not only inform, they foreclose and discourage use that provides significant health benefits. As set forth in the concrete examples discussed in Section II below, the consequences of striking the wrong balance on the side of excessive caution and overwarning can be as injurious to the public health as those on the side of underwarning.

FDA subjects prescription drugs like Phenergan to the most detailed regulatory oversight of any product available to the public, fully as rigorous as that which the Court found preemptive in *Riegel v. Medtronic, Inc.*,

128 S. Ct. 999, 1004-05 (2008). As FDA has repeatedly explained, its judgment as to the proper labeling of prescription drugs is based on a balancing of the need to inform physicians of potential adverse events against the danger of improperly dissuading beneficial drug use. In holding to the contrary that FDA requirements "merely set minimum standards," the Vermont Supreme Court below ignored the fundamental fact that prescription drugs – notwithstanding recognized potential risks – provide significant medical benefits that dramatically improve patient health. While FDA is and should be concerned that physicians have sufficient information and instruction about a drug's potential adverse effects, FDA likewise is and should be concerned that physicians are not unduly discouraged from using medically-indicated drugs for their patients.

The risk of an excessive focus on risk is not an abstract concern. The underutilization of prescription drugs in this country poses a significant public health problem, by many accounts more significant than the risks posed by the inappropriate use of potentially dangerous drugs. This underuse of beneficial medications is often driven by overwarning of alleged safety risks. There are numerous, concrete examples of overwarning that have led to serious adverse consequences to the public health, including:

(1) An increase in the teen suicide rate following new warnings of an alleged selective serotonin reuptake inhibitor ("SSRI") antidepressant drugs/suicide link that discouraged physicians from prescribing the drugs to the teenage patient population;

(2) A decrease in the IQ and other intelligence measures of babies whose pregnant mothers stopped eating fish, notwithstanding its beneficial effect on embryonic development, due to warnings of potential adverse effects of mercury contained in the fish;

(3) An increase in abortions following a "pill scare" caused by warnings in Europe of alleged increased risks of venous thrombosis arising from third generation oral contraceptives; and

(4) A resurgence of measles attributed in part to the decision by a small subset of parents to forgo vaccinations for their children because of fears of a link between the vaccines and autism.

As the expert body established by Congress to determine drug safety and labeling, FDA is charged with pursuing a balanced regulatory approach that weighs the consequences of both understating and overstating drug risks, and – as it did in determining that Phenergan should be available for use by direct intravenous injection with precisely approved warnings – FDA seeks to avoid imposing labeling requirements that would do more harm than good to the public health. A jury sitting in judgment of a single plaintiff's personal injury tort claim does not have the expertise, the information, the responsibility, or the broader public health perspective with which to make this fundamental balancing decision.

The Court's prior preemption analyses in products liability litigation has been informed largely by two fundamental questions: (1) does the federal

government specifically regulate the product safety or labeling at issue in the state tort lawsuit? and (2) does the federal government seek to balance societal costs and benefits in establishing the federal regulatory requirements at issue? Where the answer to both of these questions is yes – as it is here – the Court has consistently held that state tort claims based upon a different common law requirement are preempted.

For these reasons, WLF and ACEP respectfully request that the claim below be held preempted and that the case be remanded for entry of judgment in favor of the petitioner.

ARGUMENT

I. FDCA REQUIRES FDA TO SPECIFICALLY REGULATE DRUG LABELING BASED ON A BALANCING OF FEDERAL OBJECTIVES

A prescription drug may not lawfully be marketed in this country unless FDA makes an affirmative finding that the drug is both "safe and effective. 21 U.S.C. § 355 (2008). As the Court has explained, "[t]he determination whether a drug is generally recognized as safe and effective . . . necessarily implicates complex chemical and pharmacological considerations . . . within the peculiar expertise" of FDA. *Weinberger v. Bentex Pharms. Inc.*, 412 U.S. 645, 654 (1973). "Evaluation of conflicting reports as to the reputation of drugs among experts in the field is not a matter well left to a court without chemical or medical background." *Id.* Thus, federal courts of appeals have repeatedly held that whether a drug and its labeling are safe and effective are squarely within the primary scope of FDA's regulatory

authority.[2]

FDA's requirements as to drug safety and labeling are imposed through a regulatory scheme that closely parallels the regulatory scheme for Class III medical devices that the Court found to have a preemptive effect in *Riegel*.[3] And as with Class III medical devices, FDA's

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[2] *See, e.g., Colacicco v. Apotex, Inc.*, 521 F.3d 253, 257 (3d Cir. 2008) ("FDA is charged with promoting the public health" by, *inter alia*, "ensuring that drugs are safe and effective") (internal quotations and citation omitted); *Zeneca, Inc. v. Shalala*, 213 F.3d 161, 170 (4th Cir. 2000) ("FDA's 'judgments as to what is required to ascertain the safety and efficacy of drugs fall squarely within the ambit of the FDA's expertise and merit deference from us.'") (quoting *A.L. Pharma, Inc. v. Shalala*, 62 F.3d 1484, 1490 (D.C. Cir. 1995), and *Schering Corp. v. FDA*, 51 F.3d 390, 399 (3d Cir. 1995)); *Henley v. FDA*, 77 F.3d 616, 621 (2d Cir. 1996) (same); *Rutherford v. United* States, 806 F.2d 1455, 1461 (10th Cir. 1986) ("[T]he intent behind the [FDCA] was to give the agency primary jurisdiction to determine evidentiary matters concerning drugs about which it has a special expertise"); *United States v. Undetermined Quantities of Various Articles of Drug Equidantin Nitrofurantion Suspension*, 675 F.2d 994, 1000 (8th Cir. 1982) ("A district court is not empowered to evaluate the actual safety and effectiveness of a drug product. That determination is committed to the FDA due to its superior access to technical expertise."); *Premo Pharm. Labs. Inc. v. United States*, 629 F.2d 795, 803 (2d Cir. 1980) (question whether a drug is safe and effective "is to be determined by the FDA which, as distinguished from a court, possesses superior expertise, usually of a complex scientific nature, for resolving the issue").

[3] "The substantial similarity between the premarket approval [for medical devices] and new drug application processes compels the conclusion that the latter also establishes a federal requirement with respect to labeling that can have preemptive effect." *Kanter v. Warner-Lambert Co.*, 99 Cal. App. 4th 780, 794 (2002); *see also Brooks v. Howmedica*, 273 F.3d 785, 789 (8th Cir.

determinations as to which drugs should be approved and the proper labeling of such drugs reflects "a cost-benefit analysis" in which FDA balances how many "lives will be saved" by the drug against the "risk of harm." *Riegel*, 128 S. Ct. at 1008.

The need for FDA to pursue this balanced approach was recognized by Congress in its amendment of the Food, Drug, and Cosmetics Act in 1962. As set forth in the Senate Report accompanying the 1962 Amendments, the new drug application approval procedures were designed to "strike [ ] a balance between the need for government control to assure that new drugs are not placed on the market until they have passed the relevant tests and the need to insure that government control does not become so rigid that the flow of new drugs to the market, and the incentive to undergo the expense involved in preparing them for market, become stifled." Drug Amendments of 1962, S. Rep. No. 87-1744 (1962), *as reprinted in* 1962 U.S.C.C.A.N. 2884.

In enacting the 1997 FDA Modernization Act, Congress reaffirmed this basic principle, declaring "a clearly defined, balanced mission for the FDA" which reflects both the federal objectives of "protecting the public health by ensuring that the products [FDA]

2001) (noting that Class III medical devices on the market prior to enactment of the Medical Device Amendments "were deemed to have PMA approval if they had gone through the NDA approval process") (citing 21 U.S.C. § 360j(l)(3)(A)). The many detailed requirements imposed by FDA on prescription drugs are fully addressed in Petitioners' merits brief and accordingly will not be reiterated here.

regulates meet the appropriate FDA regulatory standards" and of "taking appropriate action on the marketing of regulated products in a manner that does not unduly impede innovation or product availability." Food and Drug Administration Modernization Act of 1997, S. Rep. No. 105-43 (1997), as printed in 1997 WL 394244, at *2-*4; *see also id.* at *10 (mission statement added to FDCA because "[c]lear statutory guidance is needed to assist the Agency to find this delicate balance"). Congress instructed: "the agency should be guided by the principle that expeditious approval of useful and safe new products enhances the health of the American people. Approving such products can be as important as preventing the marketing of harmful or ineffective products." *Id.* at *8, *15. This balanced mission statement is set forth in FDA regulation, 21 U.S.C. §§ 393(b)(1) & (b)(2)(b) (2008),[4] and is reflected in the Court's discussion in *Buckman* of FDA's "often competing" regulatory objectives. *Buckman v. Plaintiffs' Legal Committee*, 531 U.S. 341, 348, 349-50 (2001).[5]

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[4] FDA is charged under these regulations with "promot[ing] the public health by promptly and efficiently reviewing [drug manufacturers'] clinical research and taking appropriate action on the marketing of regulated products in a timely manner" and "protecting the public health by ensuring that...drugs are safe and effective." 21 U.S.C. §§ 393 (b)(1) & (b)(2)(b) (2008); *see also Colacicco*, 521 F.3d at 253.

[5] *See also* Final Rule, New Drug and Antibiotic Regulations, 50 Fed. Reg. 7452-01, 7452 (Feb. 22, 1985) ("the final regulations [the NDA rewrite] enable FDA to act as *both a public health promoter*, by facilitating the approval of important new safe and effective therapies, and as a *public health protector*, by keeping off the market drugs not shown to meet safety and efficacy

Like the Department of Transportation in its regulation of automobile air bags in *Geier v. Am. Honda Motor Co.*, 529 U.S. 861, 874 (2000), FDA has rejected "the more ... the better" approach in achieving its federal objectives with respect to prescription drug warnings. In the preamble to its January 2006 Final Rule on prescription drug labeling, FDA explained that it seeks to achieve a balance in drug warning labels. FDA cautioned that drug labels that include overly aggressive warnings could both (1) undermine the effectiveness of other, FDA-approved warning language and (2) discourage the use of medically-appropriate drug treatments to the detriment of patient health. *See* Final Rule, Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products, 71 Fed. Reg. 3922 (Jan. 24, 2006).

FDA first explained that more warnings can often translate into less effective warnings. "[L]abeling that includes theoretical hazards not well-grounded in scientific evidence can cause meaningful risk information to 'lose its significance.'" *Id.* at 3935. FDA noted that adopting a simplistic, "more is better" approach can lead to an overcrowding of labels that "limit physician appreciation of potentially far more significant contraindications and side effects." *Id.* The Eighth Circuit Court of Appeals has recognized the legitimacy of these FDA concerns:

> There are . . . a number of sound reasons why the FDA may prefer to limit warnings on product labels. Warnings about dangers

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standards.") (emphasis added).

> with less basis in science or fewer hazards could take attention away from those that present confirmed, higher risks. A label with many varied warnings may not deliver the desired information to users.

Brooks v. Howmedica, 273 F.3d 785, 796 (8th Cir. 2001); *see Dowhal v. SmithKline Beecham Consumer Healthcare*, 88 P.3d 1, 13 (Cal. 2004) ("Against the benefits that may be gained by a warning must be balanced the dangers of overwarning and of less meaningful warnings crowding out necessary warnings, the problems of remote risks, and the seriousness of the possible harm to the consumer."); *see also Colaccico v. Apotex, Inc.*, 521 F.3d 253, 275 (3rd Cir. 2008) (holding that FDA's assertion that "allowing unsubstantiated warnings would likely reduce the impact of valid warnings by creating an unnecessary distraction and making even valid warnings less credible" is entitled to some degree of deference).[6]

FDA next explained that excessive caution also undermines federal objectives by unduly discouraging physicians from using drug treatments that could help

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[6] FDA's concern about the danger of overly-crowded warning labels was, in fact, a primary factor behind FDA's adoption of the new rule for prescription drug labeling issued in January 2006, adding a requirement that labels include a "Highlights" section up front to direct physicians to the most significant health information. In explaining its development of the new rule, FDA explained that "[i]n recent years, there has been an increase in the length, detail, and complexity of prescription drug labeling, making it harder for health care practitioners to find specific information and to discern the most critical information." 71 Fed. Reg. at 3922.

their patients. As FDA explained, the "more is better" approach "could result in scientifically unsubstantiated warnings and underutilization of beneficial treatments." 71 Fed. Reg. at 3935. "[L]abeling that does not accurately portray a product's risks . . . [can] potentially discourag[e] safe and effective use of approved products or encourag[e] inappropriate use." *Id.* FDA cautioned:

> Given the comprehensiveness of FDA regulation of drug safety, effectiveness, and labeling under the act, additional requirements for the disclosure of risk information are not necessarily more protective of patients. Indeed, they can erode and disrupt the careful and truthful representation of benefits and risks that prescribers need to make appropriate judgments about drug use. Exaggeration of risk could discourage appropriate use of a beneficial drug.

Id. In *Riegel*, the Court recognized the reasonableness of this FDA concern. *Riegel*, 128 S. Ct. at 1008, 1009 (noting that FDA applies a cost-benefit analysis that protects the interests of patients who benefit from treatment as well as those who might be exposed to potential adverse risks); *see also Colaccico*, 521 F.3d at 275 (noting FDA's view that "[u]nder-use of a drug based on dissemination of unsubstantiated warnings may deprive patients of efficacious and possibly lifesaving treatment").

FDA's explanation of its efforts to avoid the potential adverse public health consequences of a "more is better" approach to prescription drug labeling should

substantially inform the Court's analysis whether the state tort law claims here at issue conflict with or frustrate FDA regulatory determinations, regardless how the Court views the separate question of what deference is due FDA's legal position on preemption.[7] As the *Colaccico* Court recognized, "the FDA's summary of its scientific determinations must be distinguished from the agency's construction of a statute, as the review of scientific information is strictly within its expertise." 521 F.3d at 270. Moreover, "FDA's view that the imposition of liability under state law for defendant's alleged failure to warn *would* interfere with FDA's accomplishment of regulatory objectives is in our view entitled to at least as much deference, if not more, as the FDA's view of its preemption authority." *Id.* (internal quotations and citations omitted).

II. RECENT SCIENTIFIC AND MEDICAL STUDIES CONFIRM THE ADVERSE PUBLIC HEALTH CONSEQUENCES OF OVERWARNING

FDA's analysis of the potential adverse health consequences of the "more is better" approach to drug warnings is not based upon theory or abstract impressions. Medical researchers repeatedly have confirmed that the underuse of prescription drugs creates public health risks at least as significant as those of inadequate physician understanding of potential adverse drug reactions. Indeed, FDA has been

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[7] *Amici* believe that FDA's preemption position is entitled to deference. This issue has been cogently addressed by FDA in its prior *amicus* brief in this case, however, and accordingly is not discussed further herein.

confronted on numerous occasions with these real-world adverse consequences when it errs on the side of caution.

In a recent study out of the Harvard Medical School, investigators analyzed pharmacologic care in a random sample of 3,457 patients in 12 metropolitan areas in the United States and determined that "[w]hen medically indicated, appropriate medications were prescribed 62.6% of the time, suggesting significant underuse of appropriate medications." William H. Shrank, et al., *The Quality of Pharmacologic Care for Adults in the United States*, 44(10) Medical Care 936, 940 (2006). By contrast, under-appreciation of drug risks was less of a problem: physician "[p]erformance was highest in avoiding use of inappropriate, potentially harmful medications (83.5%)." *Id.* In discussing their findings, the researchers explained that "[u]nderuse of appropriate medications comprised more of the quality deficiencies than prescribing potentially harmful medications. These findings suggest that focusing solely on reducing medication errors, although a laudable goal, may miss the largest proportion of quality deficits in pharmacologic care." *Id.*; *see also id.* at 943 (discussing study results and results of earlier study of drug use in the elderly and noting "the message in both studies is the same; underuse represents a more pervasive problem than overuse of potentially hazardous drugs, and deficits exist throughout the prescribing continuum").

While there likely are a number of factors contributing to drug underutilization, medical researchers in peer-reviewed publications repeatedly have pointed to unfounded safety concerns as a driving

factor. For example, in 2005, investigators reported that "[s]everal reviews of hospital discharge data revealed that β-adrenoceptor antagonists remain significantly underutilized in patients with acute, as well as chronic coronary artery disease" and that "[m]isconceptions about the adverse effects and who would benefit probably account for physician reluctance to prescribe these medications." Michael A. Gutierrez & Arthur J. Labovitz, *Underutilization of β-Adrenoceptor Antagonists Post-Myocardial Infarction,* 5(1) Am. J. Cardiovasc. Drugs 23, abstract (2005). Another recent article discussed the barriers to effective migraine care caused by misperceptions of alleged adverse effects of prescription drug triptans. Richard Wenzel, *Migraine Headache Misconceptions: Barriers to Effective Care,* 24(5) Pharmacotherapy 638, 641 (2004) ("the vasoconstrictor effects of triptans on coronary vasculature are clinically insignificant . . . withholding of these agents from patients who may otherwise benefit, for fear of cardiac consequences, is unjustified"). And yet another article examined how misperceptions regarding alleged teratogenic risks deprive women in the United States of medically-appropriate treatment for nausea and vomiting in pregnancy. Gideon Koren & Zina Levichek, *The Teratogenicity of drugs for nausea and vomiting of pregnancy: Perceived versus real risk,* 186(5) Am. J. Obstet. Gynecol. 5248, 5252 (2002) ("in this study, we have provided evidence that because of misinformation and misperception relating to teratogenic risk, the majority of women with [nausea and vomiting of pregnancy] do not receive appropriate pharmacological or nonpharmacological treatment for this condition").

Over the past few years, FDA has been faced with

a number of specific examples of how the "more is better" approach to warnings can lead to significant adverse public health consequences. While one might debate the particulars of the warnings provided in each particular case, these examples clearly illustrate the dangers of overwarning and provide a compelling explanation why FDA under FDCA establishes both a ceiling and a floor in requiring specific drug labels. Plaintiffs' conflicting "more is better" minimum standards approach can lead to serious injury to the public health.

A. SSRI Drug Warnings Lead to Increased Incidence of Suicide

Over the past twenty years, various plaintiff advocacy groups have pressed FDA to require warnings on antidepressant selective serotonin reuptake inhibitor (SSRI) drugs of a purported causal relationship with suicide and suicidal ideation. FDA repeatedly rejected the proposed warnings as scientifically unsubstantiated. In 2003 and 2004, however, a reanalysis of certain clinical trial data led FDA (and certain European regulators) to issue public health warnings about a possible association between SSRI drugs and increased suicidal thinking in pediatric patients and young adults.

Recently published research on the use of SSRI drugs and suicide rates suggest that these new warnings had a perverse effect – the incidence of suicide increased, not decreased, following their issuance. In the September 2007 issue of the *American Journal of Psychiatry*, a group of scientists supported by grants from the National Institute of Mental Health announced the findings of a targeted study of the impacts of the

SSRI warnings on suicide rates.[8] The study examined SSRI use and suicide rates following increased warnings in drug labels in the United States and the Netherlands. The findings were dramatic. In both the United States and the Netherlands, the new warnings led to significant decreases in SSRI use in pediatric patients and concomitant sharp *increases* in suicide rates in that population (reversing a long trend of decreasing suicide rates). Conversely, in patients above 60 years of age, where doctors had not been warned against SSRI drug use, the use of these medications continued to increase and the suicide rate continued to decrease. While noting that their findings were preliminary, the researchers concluded: "If the intent of the pediatric black box warning was to save lives, the warning failed, and in fact it may have had the opposite effect; more children and adolescents have committed suicide since it was introduced. If as a result of extending the black box warning to adults there is a 20% decrease in SSRI prescriptions in the general population, we predict that it will result in 3,040 more suicides (a 10% increase) in 1 year."[9]

B. Warnings Against Fish Consumption In Pregnancy Lead to Lower Child IQ Scores

Fish and seafood are the major dietary sources of

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[8] Robert D. Gibbons et al., *Early Evidence on the Effects of Regulators' Suicidality Warnings on SSRI Prescriptions and Suicide in Children and Adolescents*, 164 Am. J. Psychiatry 1356 (2007).

[9] *Id.* at 1361-62.

omega-3 fatty acids – especially a substance called docosahexaenoic acid – which are key nutrients for the brain and nervous system in developing fetuses, infants, and young children. Accordingly, many scientists and physicians believe that pregnant and breastfeeding women should follow a diet rich in fish and seafood. However, concerns that seafood was contaminated with mercury led FDA and EPA to issue consumer advisories in 2001 and again in 2004 warning pregnant and breastfeeding women (along with women wanting to become pregnant and young children) to eat no more than 12 ounces weekly of fish or seafood. These public advisory warnings, which were further publicized by the self-help book *What to Expect When You Are Expecting*, had an immediate impact. A study conducted in 2007 at the Medical University of South Carolina found that the warnings had caused 56% of pregnant women to cut fish consumption.[10]

In February 2007, a study published in *Lancet* found that the warnings against fish consumption in pregnancy had had the exact opposite of the intended consequence. Children of women who ate the smaller amounts of fish and seafood during pregnancy *had lower IQs and lower academic scores at age 8 and more behavioral and social problems* throughout early adolescence than youngsters whose mothers ate 12 or

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[10] *See For Pregnant Women, Benefits of Eating Ocean Fish Outweighs Concerns From Trace Levels of Mercury: Experts in Obstetrics And Nutrition Unveil Seafood Consumption Recommendations During Pregnancy*, Press release from National Healthy Mothers, Healthy Babies Coalition, *available at* http://www.brainybabieshealthykids.org/press-release-100407/.

more ounces per week.[11] On October 4, 2007, scientists with the National Healthy Mothers, Healthy Babies Coalition, a non-profit organization with 150 members including the American Academy of Pediatrics, the March of Dimes, the National Institute of Child Health and Development and the CDC, announced a sharp break from these earlier warnings, advising that pregnant and breastfeeding women should eat *at least* 12 ounces of fish and seafood per week to ensure their babies' optimal brain development.[12] The coalition scientists pointed to a growing body of evidence that selenium, a mineral that occurs in seafood at five to 20 times the concentration of mercury, may counteract potential negative influences of mercury exposure and explained that the risk of mercury toxicity is in any event quite rare as compared to the common risks of nutritional deficiency that can be counteracted by increased seafood intake.[13]

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[11] Joseph R. Hibbeln et al., *Maternal seafood consumption in pregnancy and neurodevelopmental outcomes in childhood (ALSPAC study): an observational cohort study*, 369 Lancet 578 (2007).

[12] *Seafood Recommendations During Pregnancy – October 4, 2007*, Press release from National Healthy Mothers, Healthy Babies Coalition, *available at* http://www.brainybabieshealthykids.org/seafood-recommendations-for-pregnancy.

[13] *Seafood Recommendations*, at 3 of 7.

C. Warnings Against Third Generation Oral Contraceptives Lead to Increased Rates of Abortion

On February 6, 2007, Public Citizen filed a petition with FDA seeking a ban on third generation oral contraceptives based upon an alleged increased risk of venous thrombosis as compared with second generation oral contraceptives.[14] The Public Citizen petition relied heavily on epidemiological studies conducted in the mid-1990s that have more recently been shown to be scientifically flawed and whose findings have now been rejected even by one of the original investigators.[15]

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[14] Petition to the FDA to ban third generation oral contraceptives containing desogestrel due to increased risk of venous thrombosis, available at http://www.fda.gov/ohrms/dockets/dockets/07p0044/07p-0044-cp00001-01-vol1.pdf. On July 25, 2007, FDA provided an interim response to the petition, explaining that it "has been unable to reach a decision on your petition because it raises complex issues requiring extensive review and analysis by Agency officials." *See* July 25 Letter from Jane A. Axelrod to Sidney M. Wolfe, available at http://www.fda.gov/ohrms/dockets/dockets/07p0044/07p-0044-let0001-vol1.pdf.

[15] *See* Walter O. Spitzer, *The aftermath of a pill scare: regression to reassurance*, 5(6) Human Reproduction Update 736, 744 (1999) (explaining that his earlier findings of increased venous thrombosis risk were entirely due to biases and confounding factors and that "[a]n integrated balanced analysis, taking into account all the cardiovascular and cerebrovascular adverse events simultaneously, favours the view that the newer third generation OC are less risky to an unselected population of women of child-bearing age than the older OC on the market"); *see also* R.F. Kaper et al., *Third- and second-generation oral contraceptives are associated with similar risk estimates for venous thromboembolism*

Beyond having scientifically shaky foundations, Public Citizen's petition invited FDA to repeat a mistake by European regulators in the 1990s that resulted in a much publicized "pill scare" among women taking oral contraceptives. While FDA properly did not take any action following the release of the now-discredited initial studies, the British Committee on Safety of Medicines issued a "Dear Doctor" letter in 1995 warning physicians of the alleged increased venous thrombosis risk. This "Dear Doctor" letter and the wide publicity it received throughout Europe led large numbers of women in European countries to stop using oral contraceptives, resulting in an increased rate of unwanted pregnancies. As a result, three European countries, Norway, the United Kingdom, and Germany, experienced a sharp increase in abortion rates in 1996.[16] As an official from the British Public Advisory Service explained, "We recognized the ramifications of that

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5 The European Journal of Contraception and Reproductive Health Care 1,12 (2000) ("Four years after the publication of the initial four epidemiological studies on [venous thromboembolism], the weight of the evidence suggests that the risk of VTE is similar for [second and third generation] OCs.").

[16] *See* D. Osterkorn & W. Schranim, *Increase in abortions following the political 'pill scare': reaction in Germany*, 3 The European Journal of Contraception and Reproductive Health 51 (1998) (reporting a relative 15% increase in the rate of abortion in women aged 15-24 years); F.E. Skeldestad, *Increased Number of Induced Abortions in Norway After Media Coverage of Adverse Vascular Events from the Use of Third-Generation Oral Contraceptive*, 55 Contraception 11 (1997) (36% increase in abortions in women aged 15-24 years in first quarter 1996 after four years of steady declines); L. Dillner, *Pill scare linked to a rise in abortions*, 312 BMJ 996 (1996) (up to 10% increase in abortions).

announcement [of the alleged increase VT risk] straight away. ... Although the government did advise women not to suddenly stop taking their pills, it seems that women did stop them abruptly because they panicked."[17]

D. Warnings Against Vaccine Lead to Outbreak of Measles

In the late 1990s, an article anecdotally linking the measles-mumps-rubella vaccine to autism resulted in a significant media outcry about the alleged dangers of the vaccine.[18] The interpretation drawing this link was subsequently retracted by most of its authors,[19] and scientific research conducted by CDC and others has now firmly established that the alleged link between the vaccine (or the preservative thimerosal used in some other vaccines) and autism/neuropsychological disorders does not exist.[20] However, the public concern over

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[17] L. Dillner, *supra* note 16 at 996.

[18] A. J. Wakefield et al., *Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children*, 351(9103) Lancet 637 (1997).

[19] *See* Simon H. Murch et al., *Retraction of an Interpretation*, 363(9411) Lancet 750 (2004) ("We wish to make it clear that in this [earlier] paper no causal link was established between MMR vaccine and autism as the data were insufficient. However, the possibility of such a link was raised and consequent events have had major implications for public health. In view of this, we consider now is the appropriate time that we should together formally retract the interpretation placed upon these findings in the paper").

[20] *See, e.g.*, Robert Schechter & Judith K. Grether, *Continuing Increases in Autism Reported to California's*

warnings of an alleged health risk of vaccines has persisted.[21]

On May 1, 2008, the Centers for Disease Control announced a resurgence of measles cases during the period January 1 to April 25, 2008.[22] CDC stated that there had been 64 confirmed cases of measles reported during this period, the highest rate of infection since

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Developmental Services System, 65(1) Arch. Gen. Psychiatry 19 (2008) (reporting increased rates of autism despite exclusion of thimerosal from vaccines); Liam Smeeth et al., *MMR vaccination and pervasive development disorders: a case-control study*, 364(9438) Lancet 963 (Sept. 11-17, 2004) (no association between MMR vaccine and autism or other pervasive development disorders).

[21] Many vaccine experts believe that the continuing misperception of an autism link was fueled by a precautionary decision by FDA to remove thimerosal from most vaccines in the late 1990s. *See* Paul A. Offit, *Thimerosal and Vaccines – A Cautionary Tale*, 357(13) NEJM 1278 (2007); *see also* Carla Williams, *Mercury-Containing Vaccine Vindicated: New Research Vindicates Thimerosal; Some Vaccine Experts [sic] Say Ban Was Premature*, ABC News (Sept. 26, 2007), *available at* http://abcnews.go.com/Health/Germs/story?id=3655803. As Dr. Paul Offit, chief of the Division of Infectious Diseases at the Children's Hospital of Pennsylvania, explained: "Although the precautionary principle assumes that there is no harm in exercising caution, the alarm caused by the removal of thimerosal from vaccines has been quite harmful." Offit, *A Cautionary Tale*, at 1279.

[22] *See* CDC Fact Sheet, *Measles – United States, January 1 – April 25, 2008*, available at http://www.wvdhhr.org/idep/pdfs/healthAlerts/talkingpoints%20for%20Measles%20Outbreak%202008.pdf.

2001.[23] CDC explained that "all but one of the current patients was unvaccinated or had an unknown vaccination history" and that "[t]he measles cases and outbreaks in 2008 result primarily from failure to vaccinate." *Id.* As reported by the Washington Post, CDC "[o]fficials, who have grown increasingly worried about parents shunning vaccines for their children because of safety concerns, said the measles outbreak illustrates the danger."[24] The 2008 resurgence follows closely on the heels of an outbreak of 34 measles cases in Indiana in 2005, which a CDC investigation likewise concluded was the result of parents refusing to vaccinate their children due to concerns over the alleged risk of autism.[25]

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[23] CDC noted that "[b]efore the measles vaccination program, about 3–4 million persons in the U.S. were infected each year, of whom 400–500 died, 48,000 were hospitalized, and another 1,000 developed chronic disability from measles encephalitis." *Id.*

[24] Rob Stein, *CDC Cites Largest Resurgence of Measles Since 2001*, WASHINGTON POST, May 2, 2008, at A2, *available at* http://www.washingtonpost.com/wp-dyn/content/article/2008/05/01/AR2008050101806.html; *see also* Jennifer Steinhauer, *Public Health Risk Seen as Parents Reject Vaccines*, N.Y. TIMES, March 21, 2008 (quoting scientist's conclusion that "[t]he autism debate has convinced these parents to refuse vaccines to the detriment of their own children as well as the community"), *available at* http://www.nytimes.com/2008/03/21/us/21vaccine.html.

[25] Amy A. Parker, *Implications of a 2005 Measles Outbreak in Indiana for Sustained Elimination of Measles in the United States*, 355(5) NEJM 447, 452-53 (2006) ("Concern about adverse events, particularly related to media reports of a putative association between vaccinations and autism and of the dangers of thimerosal, appeared to play a major role in the decision of these families to decline vaccination.").

* * * *

Any contention that FDA is not and should not be concerned with the potential adverse health consequences of overwarning on drug labels ignores the real world in which FDA operates and in which patients receive – or fail to receive – appropriate medical treatment. This danger is particularly evident here. While the risk of human error with IV-push administration of Phenergan is well recognized, medical healthcare providers often conclude that the benefits of this mode of administration for particular patients outweighs the risk. In a recent survey of nearly 1,000 healthcare providers posted on the Institute for Safe Medical Practices website, only 24% of respondents agreed with the suggestion that FDA should withdraw approval for IV administration of Phenergan.[26] Indeed, "recommendations that would eliminate the use IV promethazine [Phenergan] and remove it from the formulary received the lowest scores for both perceived value and current implementation, perhaps because there are so few alternatives as effective as IV promethazine."[27]

Particularly where, as in the case of Phenergan and IV push administration, FDA has weighed the competing public health interests and required a balanced label that seeks to ensure the continued availability of the medical treatment at issue, juries should not be allowed to impose a different "more is

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[26] Results of the Institute for Safe Medical Practices survey are available at http://www.ismp.org/newsletters/acutecare/articles/20061102.asp.

[27] *Id.*

better" requirement under state tort law.

III. THE COURT HAS CONSISTENTLY PREEMPTED STATE TORT LAW CLAIMS THAT WOULD IMPOSE REQUIREMENTS THAT DIFFER FROM THE BALANCED JUDGMENT OF THE FEDERAL GOVERNMENT

FDA's requirement that the Phenergan label provide physicians with the informed option to administer the drug through the IV push method is exactly the type of federal requirement that the Court has consistently found preemptive of state tort law claims. While the Court has confronted the question of preemption in products liability litigation in a variety of federal regulatory regimes involving both express and implied conflict preemption, the Court's analyses provide a consistent directive. In each case, the Court has asked two questions: (1) does the federal government regulate the specific conduct at issue in the underlying tort case, and (2) does the government's regulatory decision require a balancing of the risks and benefits of both less and more stringent government action. Where, as here, the answer to both questions is in the affirmative, the Court has recognized the conflict between state tort law and federal objectives, and the state tort claim has been held preempted.

A. The Federal Government's Regulatory Oversight of the Product Must Reach the Specific Conduct at Issue

The Court's determination whether federal law preempts a state tort law claim turns in the first instance on the extent to which the federal government regulates the specific conduct at issue. While the answer to this question may not be determinative, in each case where the Court has found specific federal oversight of the conduct allegedly violative of state tort law, it has held the state tort law claims preempted.

The importance of the scope of federal oversight to the Court's preemption analysis is apparent from a comparison of the Court's rulings in the medical device preemption cases of *Lohr* and *Riegel*. While *Lohr* and *Riegel* involved an express preemption provision in the Medical Device Amendments ("MDA") to the Federal Food, Drugs & Cosmetics Act ("FDCA"), and this case involves implied conflict preemption, the analytical issue before the Court is substantively identical. As Justice Breyer explained in his controlling concurrence in *Lohr*: "It makes sense, in the absence of any indication of a contrary congressional (or agency) intent, to read the [MDA] pre-emption statute . . . in light of these basic [implied conflict] preemption principles. The statutory terms 'different from' and 'in addition to' readily lend themselves to such a reading, for their language parallels pre-emption law's basic concerns." *Medtronic, Inc. v. Lohr*, 518 U.S. 470, 508 (1996) (Breyer, J., concurring). *See also Crosby v. Nat'l Foreign Trade Council*, 530 U.S. 363, 372 n.6 (2000) (preemption categories are not rigidly distinct); *Gade v. Nat'l Solid*

Wastes Mgmt Ass'n, 505 U.S. 88, 104 n.2 (1992) (same); *English v. General Electric Co.*, 496 U.S. 72, 79 n.5 (1990) (same).

Lohr and *Riegel* both addressed whether state tort claims involving medical devices were preempted by FDA's approval of those devices. The Court reached opposite conclusions on preemption in the two cases because of the far different nature of FDA regulation of the medical devices that allegedly caused plaintiffs' injuries. In *Lohr*, the Court held that state tort claims involving "substantially equivalent" medical devices approved under FDA's Section 510(k) process were not preempted because of the limited nature of FDA's oversight of such devices. The Court noted that FDA's review lasted "an average of only 20 hours," that FDA's decision approving the devices "focused on *equivalence*, not safety," and that the devices were "never . . . formally reviewed under the MDA for safety or efficacy." *Lohr*, 518 U.S. at 479, 493. By sharp contrast, the Court in *Riegel* held that common law tort claims involving Class III medical devices approved under the pre-market approval ("PMA") process are preempted because those devices are subject to rigorous FDA safety review: "While devices that enter the market through § 510(k) 'have never been formally reviewed under the MDA for safety or efficacy,' . . . the FDA may grant premarket approval [for a medical device] only after it determines that a device offers a reasonable assurance of safety and effectiveness." *Riegel*, 128 S. Ct. at 1007.

The Court's other recent preemption rulings illustrate the same point. For example, in *Bates v. Dow Agrosciences LLC*, 544 U.S. 431, 440 (2005), the Court held that tort claims based on the alleged inefficacy of a

pesticide were not preempted by EPA regulation of the pesticide under the Federal Insecticide, Fungicide, and Rodenticide Act ("FIFRA") because "EPA's approval of a pesticide label does not reflect any determination on the part of EPA that the pesticide will be efficacious or will not damage crops or cause property damage." The Court made clear, however, that state tort claims were preempted to the extent inconsistent with specific EPA requirements relating to the product. *See id.* at 453 ("For example, a failure to warn claim alleging that a given pesticide's label should have stated 'DANGER' instead of the more subdued 'CAUTION' would be preempted because it is inconsistent with 40 C.F.R. § 156.64 (2004), which specifically assigns these warnings to particular classes of pesticides based on their toxicity."). Likewise, in *Sprietsma v. Mercury Marine*, 537 U.S. 51, 65-68 (2002), the Court held that state tort claims were not preempted where the Coast Guard had decided *not* to regulate whether motorboats should have propeller guards, leaving the issue open for state regulation. On the other hand, in *Geier*, 529 U.S. at 878-81, the Court held that the plaintiff's tort claims based upon the lack of airbags in an automobile manufactured by defendant were preempted because that Department of Transportation had made the affirmative regulatory decision "that safety would best be promoted if manufacturers installed *alternative* protection systems in their fleets rather than one particular system in every car." (internal citation omitted). And the Court held fraud-on-the-FDA claims preempted in *Buckman*, 531 U.S. 341, at 348, 349, finding that "FDA has at its disposal a variety of enforcement options that allow it to make a measured response to suspected fraud upon the Administration" and that "the federal statutory scheme amply empowers

the FDA to punish and deter fraud against the Administration."

B. The Federal Government's Exercise of Its Regulatory Authority Must Reflect A Balancing of Different Federal Objectives

While specific federal oversight is a condition precedent to a finding of preemption, the federal government's exercise of that authority to achieve a balance of different federal objectives generally has been conclusive. Where a state tort claim is premised on a legal standard that differs from the balance reached under federal law, the state tort claim cannot proceed.

Again, the consequence to the Court's preemption analysis of a federal regulator having balanced competing objectives is highlighted by the Court's decisions in *Lohr* and *Riegel*. In *Lohr*, the Court rejected preemption of state tort claims involving § 510(k) devices because FDA's regulation of those devices did not reflect a balancing of federal objectives: "[t]he generality of those requirements" for Section 510(k) medical devices "make this quite unlike a case in which the Federal Government has weighed the competing interests relevant to the particular requirement in question." *Lohr*, 518 U.S. at 501. In *Riegel*, by contrast, the Court found the state tort claims preempted by FDA's balancing of federal objectives, noting that "the experts at the FDA" "apply a cost-benefit analysis," asking "How many more lives will be saved by a device which, along with its greater effectiveness, brings a

greater risk of harm?" *Riegel*, 128 S. Ct. at 1008.[28] The Court likewise focused on FDA's efforts "to achieve a somewhat delicate balance of statutory objectives" in finding preemption in *Buckman*. 531 U.S. at 348. As the Court explained, FDA "pursues difficult (and often competing) objectives," including ensuring that medical devices are safe and effective while also ensuring that they are "on the market within a relatively short period of time," and "regulating the marketing and distribution of medical devices without intruding upon decisions statutorily committed to the discretion of health care professionals." *Id.* at 349, 350.

Similarly instructive are the Court's different conclusions as to the preemptive effect of the federal regulatory schemes at issue in *Sprietsma* and *Geier*. In *Sprietsma*, the Court found the Coast Guard's decision not to require propeller guards reflected "only a judgment that the available data did not meet the [Federal Boat Safety Act's] 'stringent' criteria for federal regulation" and that the Coast Guard "most definitely did not reject propeller guards as unsafe." 537 U.S. at 66-67. The Court noted that this decision presented "a sharp contrast" with DOT's decision in *Geier*, which reflected a balancing of statutory objectives. *Id.* at 67. As the Court in *Geier* explained,

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[28] *See also Riegel*, 128 S. Ct. at 1009 ("It is not our job to speculate upon congressional motives. If we were to do so, however, the only indication available – the text of the statute – suggests that the solicitude for those injured by FDA-approved devices, which the dissent finds controlling, was overcome in Congress's estimation by solicitude for those who would suffer without new medical devices if juries were allowed to apply the tort law of 50 States to all innovations.")

where the federal government is pursuing such a balance, the "minimum standards" argument propounded by the opponents of preemption is without merit:

> In petitioners' and the dissent's view, [the DOT regulation] sets a minimum airbag standard. As far as [the regulation] is concerned, the more airbags, and the sooner, the better. But that was not the Secretary's view. ... [T]he standard deliberately provided the manufacturer with a range of choices among different passive restraint devices. Those choices would bring about a mix of different devices introduced gradually over time; and ... would thereby lower costs, overcome technical safety problems, encourage technological development and win widespread consumer acceptance – all of which would promote [the regulation's] safety objectives.

Geier, 529 U.S. at 874-75.

* * * *

The Court has never allowed a state tort claim to proceed where the federal government has regulated the specific conduct at issue and established a different legal requirement based upon a balancing of federal objectives. The Vermont Supreme Court allowed exactly such a claim to proceed in this case.

CONCLUSION

The Vermont Supreme Court's holding that FDA established only minimum standards for the Phenergan label is based upon a fundamental misunderstanding of how FDA secures federal objectives in its detailed regulation of prescription drugs. FDA's rejection of a contraindication against IV push administration on the Phenergan label reflects an informed judgment that balances the federal objectives of advising physicians of potential adverse risks while not unduly discouraging physicians from using Phenergan in a manner that provides significant health benefits to patients not before a court in tort litigation. The Vermont Supreme Court's holding that a jury could reach a different conclusion under state common law without conflicting with federal law and frustrating federal objectives is in error. Plaintiff's claims are preempted, and the judgment below should be reversed.

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Petitioner,

v.

DIANA LEVINE,
Respondent.

On Writ of *Certiorari* to the
Supreme Court of Vermont

BRIEF OF KIM WITCZAK, SARA BOSTOCK, AND HEALTHY SKEPTICISM AS *AMICI CURIAE* IN SUPPORT OF RESPONDENT

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INTEREST OF THE *AMICI CURIAE*[1]

Kim Witczak is a drug safety advocate and a newly appointed member of the FDA's Psychopharmacologic Drugs Advisory Committee ("PDAC"). In 2003, following the suicide of her husband Tim "Woody" Witczak while under the influence of the antidepressant Zoloft, she created a website, www.woodymatters.com to raise awareness of and to serve as a public resource for information concerning the risks of antidepressants and other drugs. Ms. Witczak has testified concerning drug safety and advertising, including at FDA PDAC meetings concerning antidepressant risks and suicide. She has also worked closely with other consumer advocacy organizations and with Congress on drug safety issues.

Sara Bostock and her husband Peter lost their 25-year old, Stanford-educated daughter Cecily to suicide 26 days after she began taking the antidepressant Paxil. In the wake of her daughter's death, Ms. Bostock became very active in educating first herself, and then others, to the suicide risks associated with antidepressants, particularly those in a class known as SSRIs (selective serotonin reuptake inhibitors), including Prozac, Paxil and Zoloft. She has testified at all three FDA advisory committee hearings on antidepressants and suicide and is the co-sponsor of the website, www.ssristories.com, which is a sortable database of more than 2,500 documented stories

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[1] Pursuant to Sup. Ct. R. 37.6, *amici* affirm that no counsel for a party authored this brief in whole or in part and that no person other than *amici*, their members, and their counsel made a monetary contribution to its preparation or submission. The parties have consented to the filing of this brief.

involving SSRI drugs and uncharacteristic acts of violence towards self or others.

Healthy Skepticism, established in 1983, is an international non-profit organization for health professionals and others with an interest in improving overall health. Its goals are to develop, evaluate and implement educational strategies to improve health care decision making and to promote evidence-based health care. Healthy Skepticism is particularly concerned with reducing harm caused by the misleading promotion of pharmaceutical drugs.

SUMMARY OF THE ARGUMENT

FDA began its push for conflict preemption based on hypothetical misbranding in an antidepressant/suicide case in 2002. Wyeth and the government continue to use that hypothetical in the case at bar, claiming that an added warning concerning IV-push administration would have misbranded Phenergan. But their actual practice contradicts their litigation position. Wyeth added a warning of the increased risk of suicidality with respect to its antidepressant Effexor, without prior FDA approval, in August 2003. Three years later, GlaxoSmithKline ("GSK") added its own warning with respect to its antidepressant Paxil without prior FDA approval. Although the added warnings were not based on "newly discovered evidence," but on a reevaluation of long-existing data, FDA did not pursue misbranding actions. To the contrary, FDA emphasized that drug companies were expressly allowed to strengthen warnings without prior FDA approval, and allowed the added warnings to stand for seven months (Wyeth) and a full year (GSK),

until, in each instance, it began to require additional warnings for the entire class of antidepressants.

Because the government has now filed four *amicus* briefs in three different antidepressant/suicide cases, these cases are instructive in tracking the government's position on preemption. Analysis of these briefs show that the legal position of FDA as litigator have become untethered to the actions of FDA as regulator. In the latest such brief, the government supported GSK's position in a Paxil-suicide case. By the time the government submitted its brief, the warning that GSK had added without prior FDA approval – concerning the same drug and the same adverse effect – had stood unchallenged by FDA as regulator for almost eight months. Undeterred, FDA as litigator again asserted that a hypothetical warning three years earlier would have misbranded Paxil, even though GSK had since admitted that the reanalysis of its existing data showed that the risk had been scientifically substantiated all along.

Finally, *amici* identify some real world problems in the antidepressant/suicide cases that demonstrate how the potential for profits leads drug companies to engage in actions that thwart effective regulation. These include withholding and manipulating data, disclosing positive clinical trial results while suppressing negative results, sponsoring studies to offset the commercial effects of increased warnings and even engineering a sham jury verdict. These actions greatly contribute to the inability of the FDA to protect the public health and demonstrate the danger of eliminating the valuable check that state tort litigation provides.

Drug manufacturers' knowledge of the risks of their drugs is always superior to that of the FDA. After approval of the drug, it is the drug manufacturer – not the FDA – which has the duty to comprehensively review and analyze potential hazards as the drug performs in the marketplace, *see* 21 C.F.R. §314.80(b), and to add warnings when appropriate. The issues raised by *amici* illustrate some of the dangers in conclusively assuming that FDA has discharged this duty. Preemption based on misbranding could only be appropriate if it is first shown that the manufacturer has actually proposed a strengthened warning and has provided FDA with adequate disclosure of the relevant information supporting the strengthened warning in conjunction with its CBE supplement.

ARGUMENT

I. WYETH'S ACTUAL PRACTICE CONTRADICTS ITS LITIGATION POSITION IN THIS COURT.

Wyeth claims in its brief that it would have been unlawful – in violation of FDCA and FDA regulations – for it to have provided physicians with additional warnings about the IV-push method of administration without first obtaining FDA approval. Wyeth Br. 30. It claims that it may add or strengthen a warning pursuant to 21 C.F.R. §314.70(c)(6)(iii)(A, C) "only when the change reflects newly discovered information about a drug's safety that was not previously considered by FDA." Wyeth Br. 10, 34. But Wyeth has added a warning based on a reanalysis of old information with respect to another of its drugs, the antidepressant

Effexor. Far from asserting misbranding, the FDA praised Wyeth's unilaterally strengthened warning.

A. Wyeth Adds a Warning Based on a Reanalysis of Existing Data Without Prior FDA Approval; FDA Does Not Pursue Misbranding. For many years after the initial approval of Prozac in 1987, the only mention of suicide on the labels of modern antidepressants provided that "[t]he possibility of a suicide attempt is inherent in major depressive disorder and may persist until significant remission occurs." There was no indication on any antidepressant label that the drug could be a part of the problem rather than a part of the cure. In the Fall of 2002, the FDA finally realized this might not be true.

On October 7, 2002, FDA completed its review of a supplemental New Drug Application ("NDA") submitted by GlaxoSmithKline ("GSK"), seeking approval of Paxil to treat major depressive disorder and obsessive compulsive disorder in pediatric patients.[2] The FDA reviewer, Andrew D. Mosholder, M.D., noted there were numerous adverse events "coded with terms such as hostility and emotional lability."[3] On October 10, 2002, FDA requested that GSK "reanalyze its data and better characterize the adverse events identified

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[2] Clinical Review of Pediatric Exclusivity Supplement for Paxil, FDA (October 7, 2002), *available at* http://www.fda.gov/cder/foi/esum/2004/20031s037_paxil_Clincal_BPCA_FIN.pdf.

[3] *Id.* at 6.

under the term emotional lability."[4] On May 22, 2003, GSK "responded to FDA's request, submitting a report that 'suggested an increased risk'" between Paxil and increased suicidality.[5] In response, FDA expanded the scope of its investigation and requested a reanalysis of pediatric data from other antidepressant manufacturers, including Wyeth.[6]

Prompted by FDA's request to reanalyze its existing data, Wyeth finally acknowledged a problem with its antidepressant, Effexor. On August 22, 2003, Wyeth, without prior FDA approval, sent out a "Dear Doctor" letter in which it warned of "increased reports among [pediatric patients] of hostility and suicide-related adverse events." The letter went on to state that Wyeth had "updated the prescribing information for Effexor" to warn of those increased reports of suicide risk.[7]

The suggestion that antidepressants might be associated with increased suicidal thoughts and behavior was not "newly discovered." For example, in response to citizen petitions submitted in 1990 and

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[4] *Amicus* Brief for the United States in *Kallas v. Pfizer, Inc.*, Case No. 2:04CV0998 in the United States District Court for the District of Utah, Central Division ("*Kallas Amicus*") at 16-17. A copy is available at https://ecf.utd.uscourts.gov/doc1/1831186593.

[5] *Id.* at 17.

[6] *Ibid.*

[7] "Dear Healthcare Professional" Letter from Wyeth (August 22, 2003), *available at* http://www.antidepressantsfacts.com/2003-08-22-Wyeth-Effexor-kids.pdf.

1991 seeking withdrawal of Prozac and/or a warning of this phenomenon, FDA convened a Psychopharmacologic Drugs Advisory Committee ("PDAC") to examine the issue. At the end of its consideration, the committee concluded that it had insufficient data to require a warning.[8] The PDAC announced its decision before Effexor was first approved in 1993, and Wyeth's August 2003 "Dear Doctor" letter was based on long-existing data. Although FDA did not have the data "in a way that would permit us to interpret it fully"[9] until 2003-2004,

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[8] The members of the committee acknowledged that "nobody in the agency dismisses the possibility that antidepressants in general or fluoxetine in particular may have – and I emphasize 'may' – the capacity to cause untoward injurious behaviors, acts, and/or intensify them." PSYCHOPHARMACOLOGICAL DRUGS ADVISORY COMMITTEE, FDA (Rockville, Maryland) (Sept. 20, 1991), Hearing Tr. at 126. The committee minutes are available at http://www.fda.gov/ohrms/dockets/ac/prozac/2443T1.PDF. The committee simply did not have sufficiently strong data to require a warning. *Id.* at 185 ("We agree the data are not great quality data."); *id.* at 269 ("I don't feel I have all the data"); *id* at 334 ("I felt we were working with half a deck in terms of data in that the best data we had were regarding fluoxetine [Prozac] and we had very, very few data regarding other drugs."). Nonetheless, there was an examination of some data, which could arguably constitute "disclosure of the relevant risk" under the government's suggested standard for preemption. *See* U.S. Br. 25. The failure to require a warning based on the 1991 data, compared to the strong warnings that followed FDA's initial consideration of the issue using its "standard approach" in 2003-2004, demonstrates the danger in the standard for which the government advocates. *See* Levine Br. 54.

[9] PSYCHOPHARMACOLOGIC DRUGS ADVISORY COMMITTEE WITH THE PEDIATRIC SUBCOMMITTEE OF THE ANTI-INFECTIVE DRUGS ADVISORY COMMITTEE , FDA (Bethesda, Maryland) (February 2, 2004), Hearing Tr. at 24, *available at* http://www.fda.gov/ohrms/dockets/ac/04/transcripts/4006T1.pdf.

therefore, the agency had had notice of the potential problem for years.

Far from claiming that Wyeth's action had misbranded Effexor by adding a warning beyond that approved by FDA, however, FDA emphasized that Wyeth's action was specifically permitted: "[i]t should be noted that sponsors have the authority to make changes of this nature, *i.e.*, that are perceived to strengthen labeling from the standpoint of safety, without prior approval by FDA."[10] There was no criticism that the information Wyeth had used as a basis for its "Dear Doctor" letter was not "newly discovered." Instead, FDA's statement tracked the plain language of the regulation: Wyeth had appropriately strengthened a warning without prior FDA approval. As the FDA's Director of the Office of Drug Evaluation confirmed in his testimony to Congress, FDA allowed Wyeth's added precaution to stand, unaltered, for seven months, until it began to require even stronger class-wide warnings for all antidepressants, as described below.[11]

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[10] Memorandum, Background Comments for February 2, 2004 Meeting of PDAC and Peds AC, FDA, at 11 (January 5, 2005), *available at* http://www.fda.gov/ohrms/dockets/ac/04/briefing/4006B1_03_Background%20Memo%2001-05-04.pdf.

[11] *FDA's Role in Protecting the Public Health: Examining FDA's Review of Safety and Efficacy Concerns in Anti-Depressant Use by Children, Hearings Before the Subcommittee on Oversight and Investigations, Committee on Energy and Commerce*, 108th Cong., 2nd Sess., Hearing Tr. at 85 (September 23, 2004)("Sept. 23, 2004 H.R. Hearing Tr."), *available at* http://www.access.gpo.gov/congress/house/pdf/108hrg/96099.pdf.

B. GSK Adds a Warning Based on a Reanalysis of Existing Data Without Prior FDA Approval; FDA Does Not Pursue Misbranding. Nor was Wyeth the only company to strengthen its warning of this problem. After it completed its review of the reanalyzed pediatric data, FDA acknowledged on October 15, 2004 that "[a] causal role for antidepressants in inducing suicidality has been established in pediatric patients,"[12] and requested that a warning of increased suicidality in pediatric patients be placed in a black box, which is the strongest warning FDA regulations allow, short of contraindicating the use altogether. 21 C.F.R. §201.80(e). In December 2004, FDA requested that antidepressant manufacturers reanalyze their data with respect to adult patients.

In May 2006, while the reanalysis of the adult data was ongoing, GSK issued its own warning pursuant to 21 C.F.R. §314.70(c)(6)(iii)(A). Without prior FDA approval, it sent a "Dear Doctor" letter in which it warned that "in the analysis of adults with [major depressive disorder](all ages), the frequency of suicidal behavior was higher in patients treated with [Paxil] compared with placebo," and that the difference was "statistically significant."[13] GSK's data demonstrated that a patient on Paxil was more than six

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[12] Labeling Change Request Letter for Antidepressant Medication, FDA (October 15, 2004), *available at* http://www.fda.gov/cder/drug/antidepressants/SSRIlabelChange.htm.

[13] "Dear Healthcare Professional" Letter from GSK (May, 2006), *available at* http://www.fda.gov/MedWatch/safety/2006/paroxetineDHCPMay06.pdf.

times as likely to attempt suicide as one on placebo. This dramatic increase in risk was "not based on new data," but on a reanalysis of old data.[14] Again, FDA did not initiate a misbranding action. GSK's added warning stood unchanged for a full year until the FDA again requested revised, class-wide warnings for all antidepressants.

C. Actual Practice Confirms Ms. Levine's Interpretation of the Regulations. Ms. Levine has analyzed the text of the regulations, and has concluded that they unambiguously allow a warning or instruction to be added or strengthened when appropriate, with no requirement that it be based on "newly discovered information." Levine Br. 39-43. The actual practice of Wyeth and GSK demonstrates that Ms. Levine's interpretation is correct. Furthermore, the FDA's actual reaction to the added warnings imposes a reality check on Wyeth's "dubious hypothetical" of misbranding. *See* Levine Br. 34. Wyeth could have added a stronger warning in a "Dear Doctor" letter with respect to Phenergan and IV-push, just as it did with respect to Effexor and increased suicidality. The claim that FDA would pursue misbranding against a manufacturer which provided a stronger warning has been groundless for decades, and remains so.

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[14] Report of Joseph Glenmullen, M.D. (August 10, 2007)("Glenmullen Report"), at 58, *available at* http://finance.senate.gov/press/Gpress/2008/prg061208a.pdf.

II. THE GOVERNMENT'S *AMICUS* BRIEFS IN ANTIDEPRESSANT CASES DEMONSTRATE THAT ITS LITIGATION POSITION HAS BECOME UNTETHERED TO ITS REGULATORY ACTIVITIES.

The government contends that its views on preemption are entitled to some deference under *Skidmore v. Swift & Co.*, 323 U.S. 134 (1944).[15] U.S. Br. at 26. This is only true to the extent that its views have the "power to persuade." *Gonzales v. Oregon*, 546 U.S. 243 (2006). The government's push for conflict preemption based on hypothetical misbranding of pharmaceutical drugs began when the government filed an *amicus* brief in an antidepressant/suicide case, *Motus v. Pfizer, Inc.*, 358 F.3d 659 (9th Cir. 2004),[16] and the government has now filed four different *amicus* briefs in three different antidepressant cases. An examination of these briefs is instructive. It reveals that FDA as litigator cast its preemption position in stone in 2002, and has simply repeated the same formulaic position, while FDA as regulator has made

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[15] The government also claims *Auer* deference in the interpretation of its regulations. U.S. Br. at 26. *See Auer v. Robbins*, 519 U.S. 452 (1997). Because the regulations it seeks to reinterpret are not ambiguous, however, no deference is due under this standard. Levine Br. 39.

[16] *See* O'Reilly, James T., *A State of Extinction: Does Food and Drug Administration Approval of a Prescription Drug Label Extinguish State Claims for Inadequate Warnings?*, 58 FOOD & DRUG L.J. 287, 288n.8 (2003)("Until DHHS asserted prescription drug preemption in a brief to the Ninth Circuit in late 2002, FDA had remained aloof from preemption arguments that often had been made by prescription drug manufacturers in defense of individual products liability lawsuits.").

significant changes that should have caused a change in its litigation position. The government continues its strategy in this Court.

A. ***Motus v. Pfizer.*** Victor Motus shot himself on November 12, 1998, six days after obtaining a sample pack of Zoloft from his internist.[17] The district court denied Pfizer's claim of preemption,[18] but ultimately granted summary judgment to Pfizer on other grounds (learned intermediary).[19] When Mr. Motus' widow appealed to the Ninth Circuit, the government filed an *amicus* brief in support of Pfizer, urging preemption, on September 10, 2002. The Ninth Circuit affirmed on alternative grounds, and did not address preemption.[20]

At the time of both Mr. Motus' death and the government's *amicus* brief, no antidepressant manufacturer had attempted to add a warning of the association between antidepressants and increased suicidality, and FDA had neither required nor prohibited such a warning.[21] Nonetheless, the

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[17] *Motus v. Pfizer*, Inc., 127 F. Supp. 2d 1085, 1086 (C.D. Cal. 2000), *aff'd*, 358 F.3d 659 (9th Cir. 2004).

[18] *Ibid.*

[19] *Motus v. Pfizer*, Inc., 196 F. Supp. 2d 984 (C.D. Cal. 2001), *aff'd*, 358 F.3d 659 (9th Cir. 2004).

[20] *Motus v. Pfizer*, Inc., 358 F.3d 659 (9th Cir. 2004).

[21] This Court's opinion in *Sprietsma v. Mercury Marine*, 537 U.S. 51 (2002), which was issued soon after the government filed the *Motus amicus*, forecloses preemption where agencies neither require nor prohibit a warning. The lack of a requirement

government – in an *amicus* brief written by Daniel Troy, a former attorney for Pfizer and counsel of record for Wyeth's *amicus* DRI in the case at bar – took the position not only that FDA had not yet required a warning, which was true, but that an added warning would have misbranded Zoloft.[22] This is the same "dubious hypothetical" conflict Wyeth claims in the case before the Court. Levine Br. 34.

Of greater long-term interest was the government's characterization of misbranding as a "self executing statutory prohibition," citing this Court's opinion in *Geier v. American Honda Motor Co.*, 529 U.S.

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or prohibition in 1998 (the year Mr. Motus died) and 2002 (the year the government filed its *amicus* brief) is clear from the FDA's statements in 2004. When the FDA's advisory committee convened to examine the reanalyzed pediatric data in February 2004, the chairman observed that "we do not believe that this data until now has been provided to us in a way that would permit us to interpret it fully." PSYCHOPHARMACOLOGIC DRUGS ADVISORY COMMITTEE WITH THE PEDIATRIC SUBCOMMITTEE OF THE ANTI-INFECTIVE DRUGS ADVISORY COMMITTEE , FDA (Bethesda, Maryland) (February 2, 2004), Hearing Tr. at 24, *available at* http://www.fda.gov/ohrms/dockets/ac/04/transcripts/4006T1.pdf. In an interview following the advisory committee's meeting, the Director of the FDA's Division of Neuropharmacological Drug Products underscored that "there's more or less standard approaches to various things. And there hasn't been one for suicidality to date." Transcript of Post-PDAC Interview with Drs. Russell Katz and Robert Temple of the FDA (February 2, 2004) at 000028, *available at* https://ecf.wyd.uscourts.gov/doc1/2071540017.

[22] *Amicus* Brief for the United States as *Amicus Curiae* in Support of the Defendant-Appellee at 15, *Motus v. Pfizer*, Inc., 358 F.3d 659 (9th Cir. 2004)("Motus *Amicus*"), *available at* 2002 WL 32303084.

861 (2000).[23] *Geier* does not stand for such a proposition. The conflict asserted in *Geier* did not involve misbranding at all, and misbranding is far from "self executing." As Ms. Levine has explained, Levine Br. 33, and this Court has previously recognized, misbranding must be asserted and proven in federal court, and "juries necessarily pass on allegations of misbranding." *Bates v. Dow Agrosciences LLC*, 544 U.S. 431, 452 (2005).[24] As subsequent events have demonstrated, certain factions within the FDA were setting the stage for replacing FDA's decades-old view – that federal regulation and state law tort suits were complementary pieces in an overall system of consumer protection – with the current position that "FDA's judgment" is the alpha and omega of drug regulation. The reversal of FDA's historical position continues into this case. U.S. Br. 9, 19, 21.

B. ***Kallas v. Pfizer.*** Shyra Kallas was 15 years old when she went to her family physician complaining of warts, and mentioned in the course of the examination that she had been having trouble sleeping and felt overwhelmed with her school work.[25]

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[23] *Id.* at 19.

[24] "FDA's judgment" is only the first step in establishing misbranding because "the FDA has no authority to declare, *ipse dixit*, that a label is false and misleading. Rather, the government must initiate an enforcement action to establish that the drug is in fact misbranded." *Witczak v. Pfizer, Inc.*, 377 F.Supp.2d 726, 730 (D. Minn. 2005). Whether a drug is in fact misbranded is determined by a jury, after a trial. *See Bates v. Dow Agrosciences LLC*, 544 U.S. 431, 451-52 (2005). *See* Levine Br. 33.

[25] The operative facts in this paragraph are set forth in the Complaint in *Kallas v. Pfizer, Inc.*, Case No. 2:04CV0998 in the

Her physician diagnosed depression, and prescribed Zoloft. Her initial prescription was written on October 8, 2002. She shot herself on November 4, 2002. The government filed an *amicus* brief claiming preemption in the district court on September 15, 2005.

The prescription to Shyra Kallas was "off-label." None of the modern antidepressants were approved to treat depression in pediatric patients as of October 2002.[26] As of October 2002, the FDA had approved only one use of one antidepressant by pediatric patients. Zoloft was "approved for treating pediatric patients only if they have obsessive-compulsive disorder."[27] Shyra

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United States District Court for the District of Utah, Central Division, at 8, available at https://ecf.utd.uscourts.gov/doc1/1831543413.

[26] Prozac was approved for treatment of pediatric depression on January 3, 2003. Efficacy Supplements Approved in Calendar Year 2003, FDA, *available at* http://www.fda.gov/cder/rdmt/ESCY03AP.HTM. It remains the only antidepressant that has demonstrated any effectiveness in treating depression in pediatric patients. "FDA emphasizes that, for the 7 drugs evaluated in pediatric major depressive disorder (MDD), data reviewed by FDA were adequate to establish effectiveness in MDD for only one of these drugs, Prozac (fluoxetine)." FDA Public Health Advisory, *Reports of Suicidality in Pediatric Patients Being Treated with Antidepressant Medications for Major Depressive Disorder (MDD)*(October 27, 2003), *available at* http://www.fda.gov/cder/drug/advisory/mdd.htm.

[27] Historical Information on Sertraline Hydrochloride (Marketed as Zoloft)(July 19, 2006), *available at* http://www.fda.gov/cder/drug/infopage/sertraline/historical.htm. Zoloft was approved for the treatment of pediatric OCD on September 20, 2002. Letter from FDA to Pfizer Pharmaceuticals (September 20, 2002), *available at* http://www.fda.gov/cder/foi/appletter/2002/20990Se802,04,19839

Kallas was not diagnosed with OCD. Thus, the FDA had not determined the safety or efficacy of Zoloft in treating her symptoms.

From a safety standpoint, moreover, the FDA had already seen black clouds on the horizon concerning antidepressants at the time of Shyra Kallas' prescription. An FDA reviewer completed his review of the Paxil pediatric data on October 7, 2002,[28] the day before her prescription. The reviewer commented that "[t]he most prominent adverse reactions not seen in corresponding adult trials appear to involve behavioral effects; these events were coded with terms such as hostility and emotional lability. As previously noted, the sponsor's method of coding these events was potentially confusing, and thus additional information will be helpful for the purpose of definitively assessing the potential behavioral toxicity of [Paxil] treatment in pediatric populations."[29] On October 10, 2002 – two days after Shyra Kallas' prescription and almost a month before her death – FDA requested that GSK "reanalyze its data and better characterize the adverse events identified under the term emotional lability."[30] This ultimately led to the FDA's requesting reanalyses

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SE8-034,036LTR.pdf.

[28] Clinical Review of Pediatric Exclusivity Supplement for Paxil, FDA (October 7, 2002), *available at* http://www.fda.gov/cder/foi/esum/2004/20031s037_paxil_Clincal_BPCA_FIN.pdf. Note that none of the three clinical studies GSK submitted showed that Paxil was effective in treating pediatric depression.

[29] *Id.* at 6.

[30] *Kallas Amicus* at 16-17.

from all antidepressant manufacturers, which in turn led Wyeth to strengthen its warnings for Effexor without prior FDA approval.

By the time the government filed its *amicus* brief on September 15, 2005, it had been almost a full year since FDA had concluded that "[a] causal role for antidepressants in inducing suicidality has been established in pediatric patients,"[31] and had requested that a warning of the same side effect that led Shyra Kallas to take her own life be placed on all antidepressant labels, in a black box.

Thus, Shyra Kallas (1) was a pediatric patient, (2) who was prescribed Zoloft for an indication as to which FDA had made no evaluation of safety and efficacy, (3) immediately after FDA had noticed a significant number of adverse events in the Paxil pediatric data, and two days before its letter asking GSK to explain them. The government filed its *amicus* brief a year after FDA had announced a causal relationship between antidepressants and increased suicidality in pediatric patients, and almost a full year after FDA had begun to require black box warnings of the same adverse event that resulted in Shyra Kallas' death. Nonetheless, the government repeated the litigation position it had taken in *Motus*, transforming its claim that misbranding was "self executing" into a mantra: "in FDA's judgment."[32] It claimed that the

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[31] Labeling Change Request Letter for Antidepressant Medication, FDA (October 15, 2004), *available at* http://www.fda.gov/cder/drug/antidepressants/SSRIlabelChange.htm.

[32] *E.g.*, *Kallas Amicus* at 26, 34, 38.

same warning the FDA had since required to be placed in a black box "would have misbranded the drug" if given two years earlier.[33] This is absurd. Courts that had analyzed the *Motus amicus* brief had not anticipated such a disconnect between FDA's legal positions and its regulatory activities.[34]

C. *Colacicco v. Apotex, Inc. I.* Lois Colacicco's physician prescribed Paxil for her depression on October 6, 2003, and her prescription was filled with

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[33] *See Kallas Amicus* at 34, 38. The government minimized its post-October/November 2002 regulatory history by "freezing" the misbranding determination at the time of prescription/suicide. "But Shyra Kallas' death preceded FDA's receipt of the May 2003 Paxil report, FDA's request for and receipt of additional information from antidepressant New Drug Application sponsors, Columbia University's reclassification of the sponsors' data, and FDA's preliminary and subsequent analysis of the sponsors' data. Thus, in October/November 2002, FDA did not believe that there was reasonable evidence of an association between Zoloft and an increased risk of suicidality in either adult or pediatric patients." *Id.* at 36.

[34] *E.g., Witczak v. Pfizer, Inc.*, 377 F.Supp.2d 726, 730 (D. Minn. 2005)("[T]he FDA has since distanced itself from the substance of the *Motus* brief by recommending labeling changes that, in fact, reflect concerns about the association between SSRIs and suicidality. Thus, the Court has 'reason to suspect that the [*Motus* brief's] interpretation does not reflect the agency's fair and considered judgment on the matter in question.'"[*quoting Auer v. Robbins*, 519 U.S. 452, 462(1997)]); *Cartwright v. Pfizer, Inc.*, 369 F.Supp.2d 876, 885-86 (E.D. Tex. 2005)("Given the hearings by both Congress and the FDA regarding suicidality, the FDA's PDAC's recent decision to recommend black box warnings regarding suicidality in children and adolescents, and the numerous experts who have concluded that there is a link between SSRIs, like Zoloft, and suicidality, it would be **inconceivable** to this Court to argue that an additional warning regarding suicidality would be false or misleading." [boldface added]).

its generic equivalent. *Colacicco v. Apotex, Inc.*, 521 F.3d 253, 256-57 (3rd Cir. 2008). She killed herself three weeks later.

More than two years before the prescription to Ms. Colacicco, the only jury that has ever evaluated the relationship between Paxil and increased suicidality in adults found that Paxil "can cause some individuals to commit homicide and/or suicide." *Tobin v. SmithKline Beecham Pharm.*, 164 F.Supp.2d 1278, 1287-88 (D.Wy. 2001).[35] The district court found the plaintiffs' evidence "scientifically reliable" and "legally admissible" under *Daubert v. Merrill Dow Pharm., Inc.*, 509 U.S. 579 (1993), both before trial and after. *Id.* at 1283.

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[35] Wyeth's *amicus* DRI has cited *Tobin* as a case that "cannot be squared with FDA's scientific determinations and its role as the expert agency under the FDCA." DRI Br. 26. As discussed *supra* at 9, GSK's own data reveals that adults taking Paxil are more than six times as likely to experience increased suicidal behavior as patients taking placebo. GSK hid this risk for more than a decade by manipulating the data it submitted to the FDA, leading the ranking member of the Senate Committee on Finance to accuse it of having "bamboozled the FDA" *see infra* at 24; it narrowly escaped criminal prosecution in Great Britain, *see infra* at 25, n.46; it was sued by the state of New York for fraudulently withholding information about the safety and efficacy of Paxil for children and adolescents and quickly settled, *see infra* at 27; and it remains under investigation by the U.S. Department of Justice, *see infra* at 24, n.44. Quite contrary to DRI's claim, the *Tobin* verdict and other similar cases filed against GSK in the past several years demonstrate clearly that tort suits are necessary to "serve as a catalyst" in the evolution of drug labeling. *Bates v. Dow Agrosciences, LLC*, 544 U.S. 431, 449 (2005). Perhaps DRI's criticism of the *Tobin* verdict can be best explained by the fact that DRI's counsel of record on its *amicus* brief, Daniel Troy, is new Senior Vice President and General Counsel for GSK, the maker of Paxil. *See* http://www.gsk.com/media/pressreleases/2008/2008_pressrelease_10085.htm.

Tellingly, GSK, the manufacturer of Paxil, did not even pursue preemption as a defense.

Two months before the prescription to Ms. Colacicco, Wyeth added its warning to pediatric patients, without prior FDA approval. The FDA did not pursue a claim against Wyeth for misbranding.

Between the time of Ms. Colacicco's prescription and the time the government filed its *amicus* brief in the district court, FDA required that the warning of increased suicidality to pediatric patients be extended to all antidepressants and that it be placed in a black box. Significantly, FDA issued public health advisories warning of the risk of increased suicidality to adult patients during this time as well.[36]

Two days before the government filed its *amicus* brief in the district court, FDA as litigator faced a true litmus test. GSK, a defendant in *Colacicco*, issued its "Dear Doctor" letter, advising that its data showed that adult patients with depression who were treated with Paxil were more than six times as likely to experience suicidal behavior as were patients treated with placebo.[37] When the government filed its *amicus* brief

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[36] FDA Public Health Advisory, *Worsening Depression and Suicidality in Patients Being Treated with Antidepressant [sic]* (March 22, 2004), *available at* http://www.fda.gov/cder/drug/antidepressants/AntidepressanstPHA.htm; FDA Public Health Advisory, *Suicidality in Adults Being Treated with Antidepressant Medications* (June 30, 2005), *available at* http://www.fda.gov/cder/drug/advisory/SSRI200507.htm.

[37] "Dear Healthcare Professional" Letter from GSK (May, 2006), *available at* http://www.fda.gov/MedWatch/safety/2006/paroxetineDHCPMay

in the district court on May 10, 2006, therefore, it was on behalf of a defendant which had issued a warning, without prior FDA approval, of the same adverse effect, to the same type of patient, two days earlier. The government noted GSK's added warning in a footnote.[38]

But the government was undeterred. It made no attempt to explain GSK's *sua sponte* warning. It simply repeated its litigation position that an added warning to Ms. Colacicco's physician would have misbranded Paxil.[39]

D. ***Colacicco v. Apotex, Inc. II.*** By the time the government filed its *amicus* brief in Ms. Colacicco's appeal to the Third Circuit on December 28, 2006, GSK's added warning had stood unchallenged for almost eight months. FDA as regulator had evaluated an actual warning, added without its prior approval by the same drug manufacturer which was a party to the litigation, concerning the same drug and the same adverse effect. It had not pursued an action for misbranding.

FDA as litigator brushed aside this inconvenient fact. This time, GSK's *sua sponte* warning made it into the text of the *amicus* brief, where FDA acknowledged

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06.pdf.

[38] Brief for *Amicus Curiae* the United States of America Defendant-Appellee at 11 n.4, *Colacicco v. Apotex, Inc.*, 432 F.Supp.2d 514 (E.D. Pa. 2006), *available at* 2006 WL 1724170.

[39] *Id.* at 13.

that it "did not reject the proposed labeling change."[40] FDA as litigator apparently decided that its failure to assert misbranding in response to an actual added warning had no effect on its hypothetical reaction to a warning that was not actually added three years earlier. The government repeated the now-ridiculous assertion that a hypothetical warning to adult patients in 2003 would have misbranded Paxil.[41]

FDA has held fast to its litigation position, even though this position has become diametrically opposed to its actions as regulator. A few years ago, certain factions within the FDA made a strategic decision to reverse FDA's decades-old position on preemption in favor of an opposite view that "FDA's judgment" is the floor and the ceiling of drug regulation. *See* U.S. Br. 19. As the circumstances of its *amicus* briefs in antidepressant/suicide cases reveal, its position has far less to do with regulatory integrity and legal analysis than with adherence to a prescribed agenda. This position has no credibility, no "power to persuade" and no legitimate claim to deference.[42]

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[40] Brief of the United States as *Amicus Curiae* in Support of Defendants-Appellees at 14, *Colacicco v. Apotex, Inc.*, 521 F.3d 253 (3rd Cir. 2008)("*Colacicco II Amicus*").

[41] *Id.* at 16, 19.

[42] The government's position on generic drugs – which carries forward to this Court in an *amicus* brief filed by the Generic Pharmaceutical Association was also curious. The generic manufacturer in *Colacicco* argued preemption on the basis that a generic manufacturer does not have a pioneer manufacturer's power under §314.70(c)(6)(iii)(A) to add a warning without prior FDA approval. But there is a federal regulation that expressly extends that power to a generic manufacturer: "The applicant shall

III. THE PROFIT MOTIVATION OF DRUG COMPANIES LEADS TO SELECTIVE AND MANIPULATED SUBMISSION OF INFORMATION, WHICH PRECLUDES EFFECTIVE REGULATION.

Preemption of pharmaceutical cases would be catastrophic because, in the real world, drug companies do not make timely, full disclosure of relevant information, in a comprehensible form, to a regulatory agency capable of processing that information in a timely and adequate manner. The promise of significant profits in the pharmaceutical industry induces drug manufacturers to manipulate submissions of data to an overworked FDA and to procure findings from scientists who depend on the drug industry to finance their research and to provide their income. Again, there are concrete examples in the antidepressant/suicide cases.

A. GSK "Bamboozles" the FDA With Respect to Suicide Data for Adult Patients. On June 12, 2008, Sen. Chuck Grassley (R-IA), the ranking member of the Senate Committee on Finance, formally asked the FDA to investigate whether GSK had

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comply with the requirements of §§314.70 and 314.71 regarding the submission of supplemental applications and other changes to an approved abbreviated application." 21 C.F.R. §314.97. Nonetheless, the government – in both *amicus* briefs it submitted in *Colacicco* – claimed that a generic manufacturer had no such power. It cited 21 C.F.R. §314.97 only in a footnote, failing to explain why it does not mean what it clearly provides. *Colacicco II Amicus* at 8 n4. Following the government's lead, the Generic Pharmaceutical Association, in its *amicus* brief in this Court, fails to cite §314.97 at all in the course of a 50-page brief claiming the same lack of power.

withheld safety information regarding the use of Paxil by adults. In his floor statement, Sen. Grassley alluded to drug companies' "hiding data," then clarified that "I don't mean that they actually hide the data. But they make these numbers so difficult to find that they might as well be invisible."[43] He concluded that "[e]ssentially, it looks like GlaxoSmithKline bamboozled the FDA."[44]

Sen. Grassley's allegations are based on GSK's improper reporting of suicidal events in adult patients in its initial NDA for Paxil, and in follow-up reports to the FDA between 1989 and 1992. The true data "demonstrates a causal link between the antidepressant and suicidal behavior. This has been true since 1989 although the 'bad' Paxil numbers obscured the risk for a decade-and-a-half."[45] GSK's manipulation of the data hid the fact that adult patients treated with Paxil are many times as likely to experience increased suicidal thoughts and behavior than patients treated with placebo, until it finally admitted to a more than six-fold increase in the risk in its May 2006 "Dear Doctor"letter – 17 years later.

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[43] Floor Statement of Sen. Chuck Grassley, *Hidden Data on Paxil* (June 11, 2008), *available at* http://finance.senate.gov/press/Gpress/2008/prg061208.pdf.

[44] *Ibid.* The Department of Justice is also investigating GSK's actions involving Paxil. Alicia Mundy, *U.S. Probe of Glaxo's Paxil Widens*, WALL ST. J., June 20, 2008, *available at* http://online.wsj.com/article/SB121393252540691395.html.

[45] Glenmullen report at 74.

B. Drug Companies Engage in Unconscionable Actions to Avoid "Commercially Unacceptable" Admissions. From the clinical trials that led to the initial approval of Paxil in 1992, there was the clue that would ultimately lead to black box warnings for all antidepressants. Buried in the small print under "Adverse Reactions: Nervous System" was a "frequent" adverse effect: "emotional lability." GSK's coding maneuver successfully hid the problem of increased suicidality for years.

Furthermore, GSK's misconduct regarding Paxil encompassed not only safety, but effectiveness as well. In 1998, GSK completed two clinical trials designed to demonstrate Paxil's effectiveness in treating major depressive disorder in pediatric patients. Neither trial showed Paxil to be more effective than placebo.[46] In an internal memo in October 1998, GSK explained that it did not disclose the results of these clinical trials because "it would be commercially unacceptable to include a statement that efficacy had not been demonstrated, as this would undermine the profile of paroxetine [Paxil]."[47]

In April 2002, GSK finally submitted the results of these clinical trials to FDA, plus a third clinical trial also concerning major depressive disorder. But it was not for the purpose of full regulatory disclosure. Under

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[46] MHRA INVESTIGATION INTO GLAXOSMITHKLINE/SEROXAT (March 6, 2008), *available at* http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON014155&RevisionSelectionMethod=LatestReleased, at 2.

[47] *Ibid.*

the provisions of the Prescription Drug User Fee Act in effect at the time, GSK was able to extend its patent on Paxil for six months if it submitted pediatric studies – even though they failed to show that Paxil was effective – prior to the expiration date. 21 U.S.C. §355a(c)(2)(A)(2002).[48] GSK gained approximately $1.6 billion in sales of Paxil by submitting studies that failed to demonstrate efficacy.[49]

The FDA reviewer predictably observed that none of the three clinical trials demonstrated that Paxil was superior to placebo in treating pediatric depression. But something else struck the reviewer in the safety data. He saw many adverse events coded "emotional lability" and asked GSK to clarify its terminology, as discussed *supra*. GSK could no longer hide its misconduct. FDA learned that "almost all of these events [labeled 'emotional lability'] related to suicidality."[50] On June 3, 2003, FDA's Dr. Russell Katz

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[48] Clinical Review of Pediatric Exclusivity Supplement for Paxil, FDA (October 7, 2002), *available at* http://www.fda.gov/cder/foi/esum/2004/20031s037_paxil_Clincal_BPCA_FIN.pdf.

[49] GSK made $3.22 billion on sales of Paxil in 2002. Pharmaceutical Executive, Special Report at 44 (May 2003), *available at* http://pharmexec.findpharma.com/pharmexec/data/articlestandard//pharmexec/182003/55215/article.pdf.

[50] *FDA's Role in Protecting the Public Health: Examining FDA's Review of Safety and Efficacy Concerns in Anti-Depressant Use by Children, Hearings Before the Subcommittee on Oversight and Investigations, Committee on Energy and Commerce*, 108th Cong., 2nd Sess., Hearing Tr. at 135 (September 23, 2004)("Sept. 23, 2004 H.R. Hearing Tr."), *available at* http://www.access.gpo.gov/congress/house/pdf/108hrg/96099.pdf.

commented that GSK "has not proposed labeling changes, and makes a feeble attempt to dismiss the finding."[51]

On June 2, 2004, the New York Attorney General filed suit against GSK, asserting that it had fraudulently withheld information on the safety and efficacy of Paxil in pediatric patients from prescribing physicians, who had written more than two million prescriptions for children and adolescents during 2002.[52] The FDA had not approved Paxil for any use by children or adolescents, so all these prescriptions were "off label." The Attorney General highlighted a pervasive problem in the clinical trials that drug manufacturers submit to FDA in conjunction with their NDAs: disclosure of positive results and suppression of negative results.[53] Specifically, he asserted that the results of the three studies of Paxil in depressed pediatric patients (which GSK had eventually revealed to the FDA on October 11, 2002) – none of which showed Paxil to be superior to placebo – were withheld from prescribing physicians. "GSK embarked on a campaign both to suppress and conceal negative information concerning the drug and to misrepresent the data it did reveal concerning the drug's efficacy and

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[51] *Id.* at 136.

[52] Complaint in *The People of the State of New York v. GlaxoSmithKline* ("N.Y Complaint"), *available at* http://www.oag.state.ny.us/press/2004/jun/jun2b_04_attach1.pdf.

[53] This practice severely undercuts the claim that the FDA reviews all relevant materials in making risk-benefit analyses on drugs. The FDA has no subpoena power, and reviews the materials that drug companies choose to submit.

safety."[54] In addition, he observed that, in all the studies that were the subject of the complaint, "GSK coded suicidal thinking and acts, as well as mood swings, crying and similar behaviors, as 'emotional lability.'"[55] In the settlement of the suit on August 26, 2004, GSK became "the first major drug manufacturer to publicly disclose information on clinical studies of its drugs."[56]

C. The Study Attempting to Correlate Decreased Antidepressant Prescriptions With a One-Year Increase in the Teen Suicide Rate Has No Credibility. To counteract the impact of the increased warnings on antidepressant sales, expert witnesses for Wyeth and other pharmaceutical companies joined forces to publish an article that

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[54] *Id.* at 8, ¶30. GSK is by no means the only antidepressant manufacturer to engage in unconscionable actions to suppress information that could affect sales. In 1995, Eli Lilly, the maker of Prozac, engineered a sham jury verdict that ultimately led the Kentucky Supreme Court to conclude that "[i]n this case, there was a serious lack of candor with the trial court and there may have been deception, bad faith conduct, abuse of the judicial process or perhaps even fraud." *Potter v. Eli Lilly & Co.*, 926 S.W.2d 449, 454 (Ky. 1996), *abrogated on other grounds*, *Hoskins v. Maricle*, 150 S.W.3d 1, 6 (Ky. 2004). Before its misconduct was discovered, however, "Eli Lilly made the verdict the centerpiece of a national publicity campaign, touting the safety of Prozac." *Winkler v. Eli Lilly & Co.*, 101 F.3d 1196, 1199 (7th Cir. 1996).

[55] N.Y. Complaint at 7, ¶25.

[56] Press Release, *Glaxo to Establish "Clinical Trials Register" With Information on All Company Drugs* (August 26, 2004), available at http://www.oag.state.ny.us/press/2004/aug/aug26a_04.html.

improperly attempted to correlate the increased warnings, decreased prescriptions and a one-year increase in the teen suicide rate in 2004.[57] Two of Wyeth's *amici* have dutifully referenced the now-discredited study as an example of "overwarning." WLF Br. 16-17; PHRMA Br. 17-18.

On its face, their argument undercuts Wyeth's primary rationale for preemption. Wyeth bases its argument on a claimed need not to second-guess the FDA's determinations of efficacy and safety. Yet, the *amici* seem to want to do exactly that when FDA requires scientifically substantiated warnings which decrease drug sales.

But the Gibbons study also fails on its merits, both because the assumptions underlying it are wrong and because the methodology is so flawed it would not be "scientifically valid" under *Daubert*.[58] The study

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[57] Robert D. Gibbons et al., *Early Evidence on the Effects of Regulators' Suicidality Warnings on SSRI Prescriptions and Suicide in Children and Adolescents*, 164 AM. J. PSYCHIATRY 1356 (2007), *available at* http://ajp.psychiatryonline.org/cgi/content/full/164/9/1356. The lead author, Robert D. Gibbons, has served as an expert witness for Wyeth, *id.* at 1362. His co-author, Dr. John Mann, is a paid consultant to at least two antidepressant manufacturers, *id.*, and served as an expert witness in *Tobin v SmithKlineBeecham*, discussed *supra* at 19. Pfizer, the maker of the antidepressant Zoloft, contributed $30,000 to the Gibbons study. *See* Alison Bass, *Suicide Rates as a Public Relations Tool*, BOSTON GLOBE, September 24, 2007, *available at* http://www.boston.com/news/globe/editorial_opinion/oped/articles/2007/09/24/suicide_rates_as_a_public_relations_tool/.

[58] The authors of ecological studies such as the Gibbons study universally agree that these studies cannot demonstrate

posits that teen suicide rates increased when

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causal relationships between antidepressant prescriptions and suicide rates. *E.g.*, Jorgen Bramness et al., *The sales of antidepressants and suicide rates in Norway and its counties 1980-2004*, JOURNAL OF AFFECTIVE DISORDERS 1, 6-7 (2007) ("Ecological studies cannot infer causality;" "the observed relationship [between declining suicide rates and antidepressant prescriptions] could be a spurious finding;" and "in times of declining suicide rates, credit for this change will be taken by different interventions"), *abstract available at* http://www.ncbi.nlm.nih.gov/pubmed/17223200?ordinalpos=2&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum; C. Barbui, *Antidepressant drug use in Italy since the introduction of SSRIs: national trends, regional differences and impact on suicide rates* SOC PSYCHIATRY PSYCHIATR EPIDEMIOL 152, 155(1999)("there does not appear to have been any dramatic reduction in overall suicide rates due to SSRI antidepressants;" "the expanded market of SSRI antidepressants does not seem to help to prevent suicide") *abstract available at* http://www.ncbi.nlm.nih.gov/pubmed/10327841?ordinalpos=2&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum; Atsuo Nakagawa et al., *Association of Suicide and Antidepressant Prescription Rates in Japan, 1999-2003* J CLIN PSYCHIATRY 908, 914 (June 2007)("We cannot infer causality from statistical associations. A fundamental limitation of this type of analysis is the lack of individual level data. It is not possible to know whether individual suicides were associated with use or nonuse of antidepressant medication. Nor is it possible to control for all variables that may contribute to observed associations, such as drug abuse and access to lethal means."), *abstract available at* http://www.ncbi.nlm.nih.gov/pubmed/17592916?ordinalpos=6&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum; Giuseppe Guaiana et al., *Antidepressant Drug Consumption and Public Health Indicators in Italy, 1955 to 2000* J CLIN PSYCHIATRY 750 (June 2005) ("[T]he analysis of long-term trends in suicide did not suggest that increases in antidepressant prescribing lie behind recent reductions in population suicides"), *abstract available at* http://www.ncbi.nlm.nih.gov/pubmed/15960569?ordinalpos=2&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum.

prescriptions of antidepressants decreased. But in 2004, the year in which suicides increased, "there was no significant drop in SSRI prescribing."[59] The lead author of the study has acknowledged that the data did not support a causal link between prescription rates and suicide in 2004: "We really need to see the 2005 numbers on suicide to see what happened."[60]

The reason that the 2005 suicide numbers were critical is that the black box warning – the alleged culprit – was implemented in early 2005, and antidepressant prescriptions did decrease that year. As it turned out, however, the rate of suicides declined in 2005. As FDA's Dr. Thomas Laughren recently confirmed, the 2005 suicide numbers "are down from where they were in 2004, and you know actually, the change in antidepressant prescribing didn't occur until 2005, so I think the only thing we can say at this point, it's not clear."[61]

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[59] Jon Jureidini, *The Black Box Warning: Decreased Prescriptions and Increased Youth Suicide?*, 164 AM. J. PSYCHIATRY 1907 (2007), *available at* http://ajp.psychiatryonline.org/cgi/content/full/164/12/1907?maxtoshow=&HITS=10&hits=10&RESULTFORMAT=1&author1=Jureidini&title=Black+Box&andorexacttitle=and&andorexacttitleabs=and&andorexactfulltext=and&searchid=1&FIRSTINDEX=0&sortspec=relevance&resourcetype=HWCIT.

[60] Alex Berenson & Benedict Carey, *Experts Question Study on Youth Suicide Rates*, N.Y. TIMES, September 14, 2007, *available at* http://www.nytimes.com/2007/09/14/us/14suicide.html?_r=3&adxnnl=1&oref=slogin&adxnnlx=1218481782-CyP+3vxr2XfE1S0RZYhiRw.

[61] JOINT MEETING OF THE PERIPHERAL AND CENTRAL NERVOUS SYSTEM DRUGS ADVISORY COMMITTEE AND THE PSYCHOPHARMACOLOGICAL DRUGS ADVISORY COMMITTEE, FDA

The conclusions in the Gibbons study are so flawed that one medical journal editor has called them "astonishing," "misleading" and "reckless," and has emphasized that the authors' findings "cannot be made from the data available."[62] Even more telling, since its publication, one of the authors of the Gibbons study has disavowed it. The author admitted the study's findings are "not right" and that it "doesn't follow from the data, it is not true and serves just to scare people. It is hard to admit this, as I am one of the authors of the article and I attached my name to it ... Maybe this time we have fallen down, and have to get up on our feet again."[63]

Finally, underlying Gibbons' conclusion is the idea that antidepressants are effective in treating

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(Beltsville, Maryland) (July 10, 2008), Hearing Tr. at 52. The committee minutes are available at http://www.fda.gov/ohrms/dockets/AC/08/roster/2008-4372r1-FDA-meeting.pdf. The authors of another similar study have expressed the same sentiment: "We feel that it is risky to draw conclusions from limited ecologic analyses of isolated year-to-year fluctuations in antidepressant prescriptions and suicides." Mark Olfson & David Shaffer, *SSRI Prescriptions and the Rate of Suicide*, 164 AM. J. PSYCHIATRY 1907-A (2007), *available at* http://ajp.psychiatryonline.org/cgi/content/full/164/12/1907-a.

[62] *See* Tony Sheldon, *Dutch Academics Criticise Suicide Claims in American Journal*, 336 BRIT. MED. J. 112 (2008), abstract available at http://www.bmj.com/cgi/content/extract/336/7636/112-b, full text available on PACER at https://ecf.innd.uscourts.gov/doc1/07111196718.

[63] Interview with Ron Herings, *Argos*, VPRO/VARA, Radio 1(December 7, 2007). A translation of the portions of the radio broadcast on antidepressant drugs and child suicide appears at https://ecf.innd.uscourts.gov/doc1/07111196719.

depression in children and adolescents. This ignores the fact that, although 36 antidepressants are subject to the current black box warning, FDA has approved only one as effective in treating pediatric depression.[64] Of the 15 pediatric clinical trials of antidepressants reviewed by the FDA, only three have shown them to be effective.[65] Even if the prescription numbers matched

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[64] FDA, *Questions and Answers on Antidepressant Use in Children, Adolescents and Adults* (May 2, 2007), *available at* http://www.fda.gov/cder/drug/antidepressants/QA20070502.htm. Despite its approval, however, even Prozac's efficacy for the treatment of children and adolescents is questionable. As Dr. Thomas Newman, an epidemiologist from UC San Francisco and FDA advisor, has explained: "We have I think very strong evidence of harm and really not very good evidence of efficacy, and although I know many practitioners are convinced that these drugs work, if you look very closely at the [Prozac pediatric] trial, just as an example, at the Childhood Depression Rating Scale, the improvement with placebo was 19 points, and the improvement with the drug was 23.4 points.... the improvement over placebo was really very, very small, and I would say not detectable by a clinician treating individual patients. ..." JOINT MEETING OF THE PSYCHOPHARMACOLOGIC DRUGS ADVISORY COMMITTEE AND THE PEDIATRIC ADVISORY COMMITTEE, FDA (Bethesda, Maryland) (September 14, 2004), Hearing Tr. at 338, *available at* http://www.fda.gov/ohrms/dockets/ac/04/transcripts/2004-4065T2.htm.

[65] JOINT MEETING OF THE PSYCHOPHARMACOLOGIC DRUGS ADVISORY COMMITTEE AND THE PEDIATRIC ADVISORY COMMITTEE, FDA (Bethesda, Maryland) (September 14, 2004), Hearing Tr. at 83, *available at* http://www.fda.gov/ohrms/dockets/ac/04/transcripts/2004-4065T2.htm. *See also* Jon Jureidini et al., *Efficacy and Safety of Antidepressants for Children and Adolescents*, 328 BRIT. MED. J. 879 (2004), *available at* http://www.bmj.com/cgi/content/full/328/7444/879; Thomas B. Newman, *A Black-Box Warning for Antidepressants in Children?*, 351 NEW ENG. J. MED. 1595 (2004), *abstract available at*

the suicide numbers – which they do not – the failure of all antidepressants except one to show effectiveness demonstrates that increased prescriptions could hardly have prevented a one-year rise in teen suicides in 2004. Simply, Gibbons' conclusions are unfounded and entirely lacking in credibility.

CONCLUSION

The judgment of the Vermont Supreme Court should be affirmed.

Respectfully submitted,

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